Application of supercritical carbon dioxide and a co-solvent in the production of polymeric film for coating of tablets

Lodhi, Alia Noor

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This thesis is submitted by

Alia Noor Lodhi

of the University of Bath
for the degree of Doctor of Philosophy
December 1995 - 1998.

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Abstract

Chlorinated and non-chlorinated solvents are used for solubilising polymers prior to coating tablets. Problems of chlorinated solvents are emissions and patient health whilst non-chlorinated solvents can contribute to degradation of the drug. The possibility of reducing the usage of chlorinated solvents in tablet coating procedures was investigated. Supercritical carbon dioxide ($scCO_2$) and a co-solvent were used as possible environmentally friendly alternative solvents. The experimental rig was verified by measuring the solubility of naphthalene in $scCO_2$.

Co-solvent addition was made by a HPLC pump, prior to entering the high-pressure pump. FDA approved methylene chloride (2.5% v/v) commonly used in tablet coating procedures was the chosen solvent.

Hydroxypropyl Methylcellulose, poly Methylmethacrylate, poly DL-lactide and poly DL-lactide-co-glycolide were studied in pure $scCO_2$ and in the $scCO_2$ - Methylene Chloride co-solvent system.

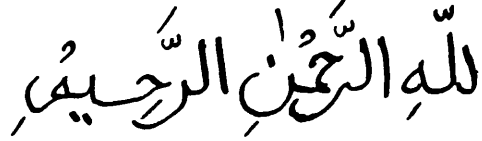
A trend of increasing solubility with increasing temperature and pressure was observed for the low molecular weight polymers such as poly D, L lactide. Increasing pressure resulted in increasing solubility in pure $scCO_2$ for high molecular weight polymers. poly Methylmethacrylate had a maximum solubility at 45°C and 600 bar, solubility then decreased with increasing temperature. Overall, the results showed that solubility of a polymer depended on the pressure and temperature of $scCO_2$, the molecular weight and the chemical nature of the polymer. The solubilities found in pure $scCO_2$ were low. However, solubility data in a co-solvent system proved to be very promising with increases of up to 500 fold at 45°C and 600 bar for the various polymers.

Preliminary studies were carried out at a temperature of 60°C, and pressures of 300 bar and 600 bar to assess the possibility of producing a thin polymeric film using poly Methylmethacrylate and $scCO_2$ -Methylene chloride system. Porous and non-porous films were successfully produced.

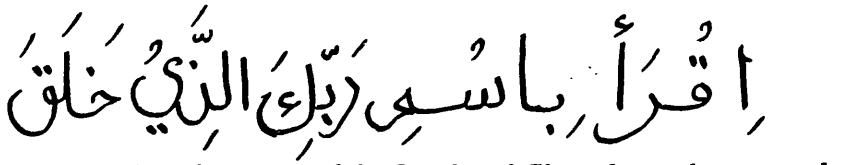
Acknowledgements

I would like to take this opportunity to thank Dr Richard England, Professor John Staniforth and Mr David Merrifield for their valuable input into my research project. My thanks are extended to the technical staff particularly, Mac Forsyth, Tony Comer, John Bishop and Ann O'Reilly for their help in building and modifying my rig.

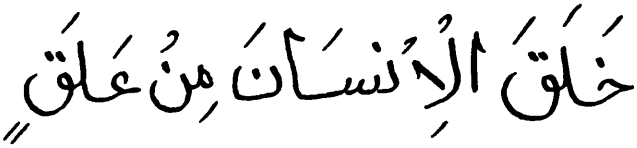
I am indebted to the Engineering and Physical Sciences Research Council and SmithKline Beecham Pharmaceuticals for the financial assistance.



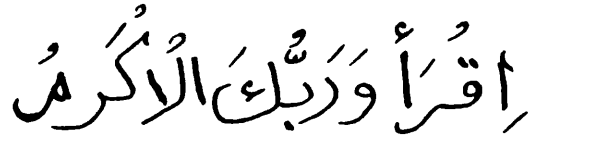
In the name of God, Most Gracious, Most Merciful



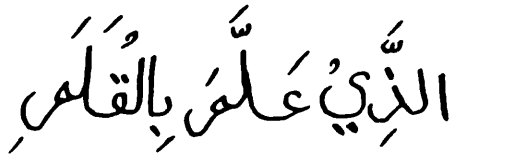
Proclaim! In the name of thy Lord and Cherisher, who created __



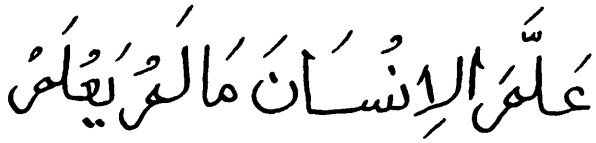
Created man, out of a mere clot of congealed blood:



Proclaim! And thy Lord is Most Bountiful, __



He who taught the use of the pen, __



Taught man that which he knew not.

Surah Alaq (SÜRA N°. XCVI)

The Holy Qur'an
Translated from Arabic by Abdullah Yusuf Ali, (1938)
Ashraf Publishers, 7 Aibak Road, Kashmiri Bazaar, Lahore, Pakistan.

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Abbreviations

Å	Angstroms
CAA	Clean Air Act
cP	centi Poise
GAS	Gas Anti-Solvent
HAP	Hazardous Air Pollutant
HPLC	High Performance Liquid Chromatography
HPMC	Hydroxypropyl Methycellulose.
HV1-4	High Pressure Valves 1-4.
$kTyr^{-1}$	kilo Tonnes per year
LV1-3	Low Pressure Valves 1-3
Mol. Wt. (Mw)	Molecular Weight
P_c	Critical Pressure
PMMA	poly Methylmethacrylate.
Ppm	concentration in parts per million.
RESS	Rapid Expansion Supercritical Solution
RTD	Resistance Temperature Device
RV1-2	Relief Valves 1-2
$scCO_2$	supercritical Carbon dioxide
SCF.	Supercritical Fluid
SEM	Scanning Electron Microscopy.
SFC	Supercritical Fluid Chromatography
SFE.	Supercritical Fluid Extraction
T_c	Critical Temperature
TLV	Threshold Limit Value.
TV1	Throttle or Micrometering Valve

1. Introduction

1.1 Aim of Project

Volatile organic compounds (VOCs) and organic solvents are a class of air pollutants that enter the environment from many sources, including chemical manufacturing and solvent evaporation during the spray application of coatings, paints, adhesives and other materials (see table 1.1). The pharmaceutical industry is responsible for 40kTyr^{-1} of VOC emissions in the UK. The major environmental impact of VOCs lies in their potential for generating ozone layer depletion via photochemical oxidation. As many VOC based solvents used in coatings are hazardous and air pollutants, much effort has been directed to developing new tablet coating systems to reduce VOC emissions in the pharmaceutical industry.

Sources	**Emissions kTyr^{-1}**
Painting Industry	278
Pharmaceutical Industry	40.0
Printing Industry	41.4
Industrial Metal Surface Cleaning	46.4
Adhesives	58.0
Oil Extraction	10.0
Agrochemical	37.4
Dry Cleaning	13.0
Other	70.0
Total	**594.2**

Table 1.1 *VOC emission from various industries.*
(Urban Air Quality in the United Kingdom, Department of Environment Report, 1993)

In this study a technique is being investigated for modifying tablet coating process ahead of any legislation enforcing alternatives to organic solvent based film coating practices. The Environmental Protection Act of 1990, however, requires general reduction in harmful waste products emitted to land, water and the atmosphere (Department of Environment, 1991).

The possibility of using supercritical carbon dioxide, $scCO_2$, as a solvent for solubilising polymers of tablet coating interest has been investigated. This project was aimed at eliminating or reducing the usage of chlorinated and non-chlorinated solvents in the tablet coating procedures, as these solvents have shown to be detrimental to the environment (Black, 1996) and long-term health of patients (Wang *et al*, 1995). Environmental damage in the form of ozone layer depletion and problems of patients health in terms of ulceration of stomach lining are attributed to the usage of chlorinated and non-chlorinated solvents in the pharmaceutical industry. The pharmaceutical industry has recognised this drawback and is investing in projects to find alternative means of solubilising a polymer prior to applying coating. It is possible that supercritical carbon dioxide may be more accommodating solvent for new and exciting drugs, which may not be stable in traditional solvents.

1.2 The need for polymeric coating

Polymeric coatings are preferred over other coatings because a thin and even film of polymer is deposited on the tablet core unlike sugar or compression coating methods (chapter 2). Tablets coated this way can be embossed or engraved with the house logo and

breaklines and these should be clearly legible after the application of coating. In addition film coated tablets perform pharmaceutical functions such as conferring enteric or controlled release (see figure 1.1).

Enteric coating protects the tablet core from disintegration in the acid environment of the stomach, whereas the controlled release polymers degrade over a particular time to prevent toxicity in a patient.

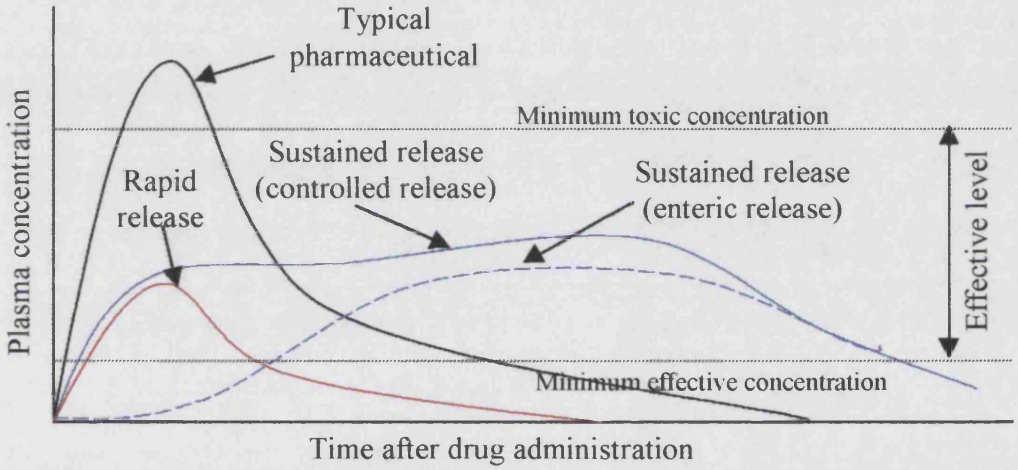


Figure 1.1 *Showing the outcome of drug release from different methods of coating a tablet.*

1.3 Possible Solvents

Currently, polymers for tablet coating are dissolved in organic or water-borne solvents prior to application. It has been shown that both organic and water-based solvents have disadvantages, which can out-weigh, their advantages. For example, with organic-borne

coatings, tablets have been known to cause chronic toxicity to patients arising from low-level residual solvents in administered tablets. This issue is of particular concern to the regulatory bodies. Chlorinated and other organic solvents are under the scrutiny of the FDA and many environmental agencies, as they can also cause damage to operators because they are flammable.

Water-borne/aqueous coatings on the other hand can lead to the hydrolysis of drug during processing. The active drug's properties change and can have adverse effect on the patient. The aqueous polymer film coating solution, use up to 90 %wt/wt water whilst the non-aqueous coating formulation can have up to 60 % wt/wt chlorinated solvents. There is a need to research into ways of avoiding or reducing the usage of water, chlorinated and organic solvents. The objective is to find environmentally friendly solvents to solubilise polymer/s prior to applying coatings.

1.4 Application of supercritical fluids as solvents

The physical properties of supercritical fluids (SCFs) are considered to be intermediate between those of liquid and gas. The most attractive feature of a supercritical fluid is the enhanced solubilising power compared to the regular gases, sensitivity to small changes in either temperature or pressure. In particular supercritical fluids have densities that are liquid-like and transport properties that are gas-like.

A small change in temperature or pressure *near* the critical point results in large changes in fluid density, viscosity and diffusivity. Table 1.2 illustrates this point of physical

properties of supercritical fluid being intermediate between gas and liquid. These favourable properties of supercritical fluids allow them to be used as powerful solvents in the field of extraction, chromatography, recrystallisation and chemical reaction (Johnston *et al.* 1988) see sections 3.4-3.6. Varying the pressure and temperature, controls the density and hence renders the fluid either more gas-like or liquid-like, this is advantageous in extraction processes. Low viscosity, a factor of 10-100 times lower than for liquids provides good flow characteristics, facilitates penetration into porous solid materials. High diffusivity leads to high rates of mass transfer and hence faster extraction than with a liquid solvent. Supercritical fluid based chromatography would be expected to be faster than for liquids but slower than a gas.

Physical State	Density ($g\ cm^{-3}$)	Viscosity ($g\ cm^{-1}\ s^{-1}$)	Diffusion Coefficient ($cm^2 s^{-1}$)
Gas	$(0.6\text{-}2.2)\times10^{-3}$	10^{-4}	0.01-1.0
SCF	0.2-0.8	10^{-3}	$(0.5\text{-}3.3)\times10^{-4}$
Liquid	0.8-1.0	10^{-2}	$(0.5\text{-}.0)\times10^{-5}$

Table 1.2 *Typical Properties of gas, supercritical fluid and liquid, (Lee and Markides, 1987)*

1.4.1 $scCO_2$ as a solvent

Supercritical Carbon dioxide was used in preference to any other supercritical fluid (see table 1.3) because of its low toxicity and environmentally acceptable status, it also has similar critical temperature and pressure parameters to the standard organic coating solvents. The latter point renders it applicable to heat labile compounds of which tablet coating polymers form one class

Water at supercritical state is highly corrosive, and on average a high quality stainless steel cell might only be expected to survive 4 hours, so it would be dangerous and uneconomical process even without considering the drug hydrolysis problem. The critical temperature and pressures of water are 374°C and 217 bar. The temperature alone is a negative factor as most of the polymers of pharmaceutical interest would degrade at these temperatures. Use of a volatile organic solvent would effectively be defeating the purpose of developing an environmentally friendly process.

Fluid	Critical Temperature, T_c (°C)	Critical Pressure, P_c (Bar)
Carbon dioxide	31.06	72.80
Nitrous oxide	36.50	72.50
Ethane, (VOC)	32.10	48.20
Ethylene, (VOC)	9.30	49.70
Propane, (VOC)	96.70	41.90
Propylene, (VOC)	91.90	45.60
Cyclohexane, (VOC)	280.30	40.20
Isopropanol, (VOC)	235.20	40.20
Benzene, (VOC)	235.20	47.00
Toluene, (VOC)	289.00	48.30
Dichloro-difluoromethane, (VOC)	111.80	40.70
Trifluoro-chloromethane, (VOC)	25.90	46.90
Ammonia	132.50	111.30
Water	374.20	217.60

Table 1.3 *Critical Parameters for some supercritical fluid solvents, (McHugh and Krukonis 1986).*

scCO₂ is environmentally compatible because it is not a volatile organic compound and it is on the Environmental Protection Agency's list of permissible emissions. Tablet coating formulators are interested in using *scCO₂* as it has physical properties close to existing organic solvents and has the potential of producing high quality coatings (Donohue *et al*, 1996).

Supercritical Carbon dioxide is an attractive solvent as carbon dioxide is a cheap, inert gas, which can escape into atmosphere. The Environmental Protection Agency for release to atmosphere approves it (Smith *et al* 1993). Supercritical carbon dioxide is emerging as a 'green' solvent in variety of industrial processes as it offers an environmentally friendly alternative to variety of organic solvents. Supercritical carbon dioxide attracts interest because it is neither toxic nor flammable, and does not threaten the ozone layer as do chlorofluorocarbons which are still used in polymer manufacturing (Black 1996). Chlorofluorocarbon solvents are classed as volatile organic compounds that are detrimental to the environment in many ways. For example, when released into the atmosphere, they facilitate destruction of ozone (O_3), a compound which is desirable in the stratosphere to block ultraviolet rays. Excessive release of chlorofluorocarbons will add to the destruction of O_3; hence a hole in the Ozone layer will result. Short-term exposure to a hole in the ozone contributes to eye, nose, and throat irritation. It can also lead to congenital birth defects (Suess *et al* 1985).

Federal, state and local authorities have become increasingly stringent on the VOC emissions in the USA. Recently, the Clean Air Act (CAA) regulations have been extended to include the emission of individual VOCs that are classified as hazardous air pollutants (HAPs). These include coating solvents, particularly those of high volatility such as

methyl ethyl ketone, methanol, hexane, toluene and xylene (Donohue *et al* 1996). Because of this great need to reduce VOC emissions, considerable effort is being put in to developing new coating technologies involving reduced levels of organic solvents.

The application of supercritical Carbon dioxide required development of a rig, which could accommodate pressure and temperature parameters of up to 600 bar and 200°C respectively. It took a year to plan, order customised items and build this unique rig. Following this it had to be pressure tested and approved as a safe apparatus. The validation tests were conducted to make sure that consistent working procedure is carried out to obtain reliable solubilities for polymers of pharmaceutical significance.

1.4.2 Use of a Co-solvent.

Preliminary studies into the solubility of tablet coating polymers have been carried out (Broadbent *et al*, 1995 and Lodhi *et al*, 1999) in the University of Bath. The results show very low solubility in pure supercritical carbon dioxide for most polymers of pharmaceutical interest. It is proposed to make use of a small percentage of a *co-solvent* such as acetone, ethanol, methanol or methylene chloride. Ekart (1993) suggests that the solubility can increase by more than 2 orders of magnitude by the presence of 2% wt/wt co-solvents including, methylene chloride and ethanol. It appears that traditionally organically based tablet coatings can be replaced by a co-solvent mixture which is rich in supercritical carbon dioxide making it less toxic to operators in the pharmaceutical industry because carbon dioxide is environmentally friendly than its predecessor. In commercial application this technique could reduce VOC emission by up to 80% and significantly

eliminate hazardous air pollutants (Busby *et al* 1991). In view of Busby *et al*'s calculations an 80% reduction in VOC emissions would lead to the production of only 8-10 kT/yr^{-1} for the pharmaceutical industry in the UK.

A co-solvent system was introduced to enhance the solubility of polymers over a range of temperatures and pressures. Methylene chloride, (dichloromethane) was the solvent of choice since it is widely used in conventional coatings and it has been described as the ideal choice of solvent for coating formulations (Jones, 1996). While this might seem to be contrary to the environmental aims of this project, it should be borne in mind that only a small percentage of co-solvent was used; in fact less than 5% v/v of methylene chloride was mixed with carbon dioxide. This percentage represents significant reduction in the amount of cholorofluorocarbons that might be released in to the atmosphere. There is, however a potential to recycle both the solvent and the co-solvent. Carbon dioxide can be recycled to eliminate its release into the atmosphere.

1.5 Data Collection

Solubility of polymers was determined in pure $scCO_2$ and in the $scCO_2$-Methleyne chloride system, following a rig validation test (see chapter 5). These were logged in graphical forms (see chapter 6) to observe and comment on trends displayed by each polymer. Full discussion on solubility and on SEM results is presented in chapter 8.

1.6 Film Production

An attempt at producing polymeric films has been made with a co-solvent system because of the significant increase in polymer solubility achieved by the addition of a co-solvent. The modifications made to rig and operating conditions are discussed in chapter 5 and films are shown in chapter 7. Scanning Electron Microscopy analysis and conventional photography was used to capture the quality of films. The production of the films demonstrates the possibility of using supercritical fluid technology for tablet coating processes. An economic appreciation of costs involved in the production of polymeric films using supercritical fluid technology will be discussed in chapter 8.

2. *Literature Review I - Tablet Coating*

2.1 Introduction

The application of a tablet coating is an additional and costly step in the tablet manufacturing process but it is a necessary process in influencing how drug is released to action site. In this chapter past and present states of coating processes are discussed - the opportunities for continued improvement are also presented. Generally the pharmaceutical industry does not develop new sugar-coated tablets due to the lengthy process, high degree of operator skills required and the fact that identification of a product is difficult. Compression coating is no longer viable because it is a slow process and core-to-coat binding is unstable. Film coating influences present day usage pattern of organic solvent and aqueous coating techniques. Organic solvent based films produce high quality coatings but suffer from serious drawbacks such as pollution, fire and safety hazards. This technique is widely used and probably will always have an application where specialised polymers are used for coating. Aqueous based film coatings come with some inherent problems too and they are still used. The pharmaceutical industry is always looking to improve and develop new coating processes because of the environmental and health issues. Development of process using a supercritical fluid as solvent for film coating could alleviate the pollution issue in the environment (see section 2.7) to name but one.

2.2 *Historical Perspective*

The coating of tablets is a very old technique. The first evidence of coating came from the *Islamic drug literature* around 850 A.D. (Sonnedecker 1980). It was an era when Arab physicians were very concerned about the presentation of drugs. Rhazes* (850-923) was one such Arab, who recommended mucilage coating using psyllium seeds. Then another equally renowned physician and philosopher Ibni Sina* (980-1037), also known as Avicenna, prepared gold and silver plated pills. Pill coating and other Arab pharmaceutical practices were adopted in Europe from about the 10th century onwards. Records show that a French physician-pharmacist, Jean du Renou* (1608) coated bitter pills by gliding them in powdered spices.

A significant breakthrough in coating came about in the late 1600s - *sugar coating* was recommended by a famous pharmacist Moyse Charas* (1676) in his *Pharmacopée Royal.* This was yet another adaptation of the Arab coating process where by Najm Uddyn made candied or preserved roots and fruits in early 900 A.D.

The French widened their research between 1837-1840 and developed a sound sugar coating/dragée; in 1837 Fortin patented a sugar coating process. In 1838 Dechamps* developed a procedure for using honey and powdered acacia to coat pills and by 1840 both a Lyon pharmacist and a Paris confectioner patented protocol which utilised a sugar solution with gum acacia.

William Warner, an enterprising Philadelphian pharmacist made sugar coated pills as early as 1856-1857, although C V Clickener* was regarded as the inventor of sugar coated pill in

the United States. An Englishman Bernard Procter* had 45 variants of the sugar coating by 1862.

The growing popularity of sugar coated pills continued right through the 1960s and early 70s, though no one fully recognised that Thomas Brockedon* had discovered *compression coating* by accident in 1843. Brokedon's small mallet fell on the metal die that punched out a single compressed tablet. It was not until 100 years later that research into production of compression coating took place (Higuchi, 1954). In 1954, Higuchi developed a compression machine, which could press 150-200 tablets a minute. A problem arose in this technique; it was not possible to control the position of the tablet core amongst the coating granules and this led to variations in disintegration time. As a result it was not a very popular coating.

Film coating was the next step forward. This came about in early 50s when Abbott Laboratories marketed the first film coated tablet (Abbott Laboratories 1956). Parallel to this invention Professor Dale Wurster at the University of Wisconsin patented an air suspension coater that effectively applied the film coating composition (Wurster 1953) to the tablet.

*Denotes that all those researchers have been discussed in Sonnedecker's article: Sonndecker G, (1980), *Pharm.. Technol.*, 4, pp77-81

2.3 Tablet Coating Principles

In the past tablet coating was seen as a trend for presenting the drug neatly. Now, however, the application has become an imperative step for the majority of the pharmaceutical tablets and the decision to coat a tablet is based on one or more of the following objectives which are presented without any order of preference:

1. to mask the unpleasant taste, odour or colour of the drug.
2. to provide physical and chemical protection for the drug.
3. to control the release of the drug from the tablet
4. to prevent the drug dissolution occurring in the gastric environment of the stomach by using an acid-resistant enteric coating. This makes the drug delivery site specific.
5. to reduce the risk of mistaken identity by colour coding and contrast printing.
6. to protect sensitive drugs from humidity, moisture, light and air.
7. to avoid incompatibilities between two drugs by including one in the film coating.

2.4 Tablet Coating Methods - Sugar Coating

Sugar coating is a multi-step process that can take from a few hours to few days depending on the operator's skill. It is very much an *art* rather than an automated chemical process. The operator determines the quantity of sugar solution to add, the method and rate of pouring, when to apply air and how long or how fast the tablets should be tumbled in the pan. A successful sugar coating process yields neat and glossy tablets.

The sugar coating process is comprised of six steps; (1) sealing, (2) subcoating, (3) syruping, (4) colouring (5) polishing and finishing (6) printing, see table 2.1 below. The tablet cores have a deep convex surface with thin rounded edges and the cores should be resistant to chipping/breakage.

Seal Coating Solution	Subcoating Powder	Syrup Solution	Polishing Solution
Cellulose acetate phthalate, Zein, Oleic acid, (USP), Propylene glycol (USP), Methylene chloride Alcohol sd 3A 200-proof PVP,	Kaolin Dextrin Cocoa Powder Calcium Carbonate, pptd, Calcium Sulfate, NF Starch, corn Talc (USP),	Sugar cane powder Starch (corn) Syrup, (USP), Water Calcium Carbonate	Carnauba, (yellow) Beewax, (white) Wax, Paraffin Naptha

Table 2.1 *A range of constituents used in Sugar Coating (Seitz 1980).*

2.4.1. Seal Coating

A seal coat is essentially applied to prevent any moisture penetrating the tablet. Often there is localised over-wetting of a portion of tablet bed and it is this moisture that is stopped from reaching the core by a seal coating. Excessive moisture can cause softening and disintegration problems and in the process physical and chemical degradation of the finished product. Sealant such as an alcohol-soluble protein derivative from corn called Zein is very effective in its role.

2.4.2. Subcoating

This layer is mainly applied to round the edges so that a smooth sugar coat can be applied and to build the tablet size. Normally subsequent coats of gelatine and acacia solutions are applied followed by a dusting of subcoating powders and drying (see table 2.1).

2.4.3. Syrup Coating

This step covers the tablets and hides any imperfections on the tablet surface. The tablets are made smooth by successive applications of dilute syrup in a coating pan (see figure 2.1a). The tablets are dried after each application.

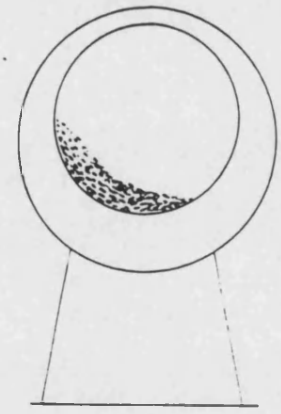


Figure 2.1a *Showing a syrup coating pan*

2.4.4. Colouring

All the sugar coated tablets are coloured only by the pharmaceutically approved colours. There are two groups of colouring substances generally in coloured tablet coatings (1)

water-soluble (2) water-insoluble pigments. The water-soluble dyes are part of the traditional method of sugar coating and their use demands a great deal of skill. Here a skilled operator's potential is evaluated in terms of how the final colour of the tablet is achieved, as numerous syrup coats are applied to adjust the colour and quality of shine. This process is prone to uneven coverage and variation in colour from batch to batch. Water-insoluble coatings such as aluminium lake or iron oxide pigments are easier to use and permit fast colouring compared to dye coating.

2.4.5. Polishing

The tablet is polished in clean standard coating pans or canvas-lined polishing pan (see figure 2.1b). The tablets receive one or two applications of wax dissolved in naphtha or other suitable *volatile* organic solvents. Usually beeswax or carnauba wax is used. The solvent is allowed to evaporate in to the air.

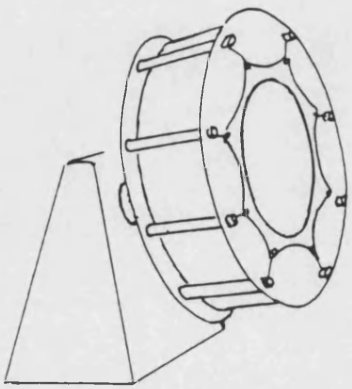


Figure 2.1b *Showing a Canvas polishing pan.*

2.4.6. Printing

The sugar coated tablets can not be embossed or engraved as the thickness of coating obliterates any core markings. Instead, the printing process used is an offset rotogravure and this is used in conjunction with edible printing inks (Lykens 1979).

2.4.7. Sugar Coating Faults

The disadvantage of sugar based coating remains the large increase in tablet size and weight which results in increased packaging and transport costs. Further limitations such as appearance of break lines, poor resistance to moisture, poor mechanical properties due to the brittle nature of the coating are all limitations that apply to sugar coated tablets. These aspects will be considered in the context of film coating. It is clear that sugar coating is not a stable coating. Generally the pharmaceutical industry does not develop new sugar-coated tablets due to the lengthy process, high degree of operator skills required and the fact that identification of a product is difficult

2.5 Tablet Coating Methods - Compression Coating

Compression coating (press-coating, dry-coating and mantel-tabletten) was developed to cut down on the long lead time of sugar coating by compressing the core and then compressing dry coating material around the core (see figure 2.2).

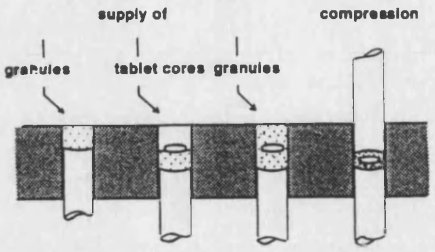


Figure 2.2 A diagrammatic representation of compression coating

Compression coating was developed in 40s and 50s after a desire to develop a coated penicillin tablet without the addition of moisture (Sandell 1983). Compression coating was also used to separate 2 drugs where the 2nd drug was added in the coating powder.

In the compression technique, there are two principal processing methods which are represented by the Killian Prescoter and Manesty Drycota (Cole, 1996). The techniques employed by the Killian machine involve the use of a separate tabletting machine to compress the cores of the tablet, which can then be fed to the single compression turret of the Prescoter by a vibratory feed system. In this case core must be relatively strong mechanically to withstand the intermediate handling. This can produce poor core-to-coat bonding, and elastic recovery of the core following recompression can cause splitting of the coat. The second processing method uses Drycota that is a twin turret machine with a synchronous transfer device, which permits preparation and coating of the cores in a single continuous operation. A further advantage is that the cores do not need to be strong, so that by controlling the porosity of the core tablet through selection of a suitable compaction pressure on the first turret, good core-to coat bonding can be achieved more easily than on

the Prescoter. This process relies on a number of very important points that include the following:

(a) The drug to be coated can be incorporated into core of no more than 12mm in diameter, the total tablet size is to be no greater than 15mm in diameter and the total tablet weight is not to be greater than 900mg;

(b) The coat bonds onto the substrate;

2.5.1. Compression Coating Faults

The disadvantages of this process are:

I. it is difficult to bond the coat and core satisfactorily;

II. core expansion causes the coat to split;

III. it is impossible to recover cores coated with this method;

IV. the process of compressing core is relatively slow, 1000 tablets per minute maximum, compared to compressing dry coating where the output is 10,000 tablets per minute maximum. Hence, machinery is not compatible enough.

2.6 Tablet Coating Methods - Film Coating

The film coating process requires that a thin film of polymer is deposited on the tablet core by a spraying method. The polymers form the basis of film coating composition. The

success of this method largely came about because of its distinct advantages such as automated system, which has led to a reduction in manpower and overall cost. The other advantages include; a thin even coat, possible controlled release, and ease of embossing/engraving house logo and breaklines. Generally the coating formulation consists of the following: *Polymer/polymers, Solvent, Plasticiser, and Colourant.* The most widely used polymer/s, solvents, plasticisers and colourants are listed in table 2.2.

Polymers	**solvents**	**Plasticisers**	**Colourants**
Hydroxypropyl Methylcellulose, (HPMC). Ethylcellulose Hydroxypropyl-cellulose, (HPC). Methylhydroxy cellulose Sodium carboxymethyl cellulose	water methanol ethanol methylene chloride methylethyl-ketone acetone chloroform	polyethylene glycol (water-insoluble) propylene glycol (water-insoluble) castor oil (water-insoluble)	Opaspray (water-insoluble) Quinoline yellow (organic), Sunset yellow (organic), Hydrated alumina (organic)

Table 2.2 *Typical film coating constituents which can be used in various combinations.*

- *Polymers*

The most commonly used polymers are the derivatives of cellulose such as Hydroxypropylmethylcellulose, HPMC, methycellulose and ethycellulose (see table 2.2). They have the advantage of forming a clear, non-tacky, mechanically strong film with a wide range of solvents. They have a history of safe use in the food industry and regulatory acceptance. Acrylate based polymers are also used in film coating. A recent development has been the introduction of a fine particle suspension of polymer e.g. ethylcellulose as a

simple coating media. The film is formed by the combined action of plasticiser and drying heat on the individual polymer particles thus causing them to coalesce into a film.

- *Solvents*

The primary function of the solvent is to dissolve or disperse the polymer and other constituents. The most widely used solvents are listed in table 2.2.

- *Plasticisers*

Plasticisers are added to film coatings to modify the physical properties of the polymer to decrease the brittleness of film. A commonly used plasticiser is poly Ethlyene Glycol, PEG (Aulton 1988).

- *Colourants*

Unlike sugar coated tablets, only water-insoluble pigments are used to overcome the specific incompatibilities that exist between dyes and film systems.

2.6.1. Atomisation in Film Coating

Atomisation is a process whereby a liquid is broken up into a spray of droplets. It is employed in a wide range of industrial processes including paint application, air-conditioning, spray drying, fluidised-bed granulation and film coating. In film coating the

atomisation technique enables the coating polymer to be efficiently applied to a sample of granule, pellet or tablets core surface. Atomised drops hit the surface in such a way that they spread evenly over the surface to form a smooth continuous film (see figure 2.3).

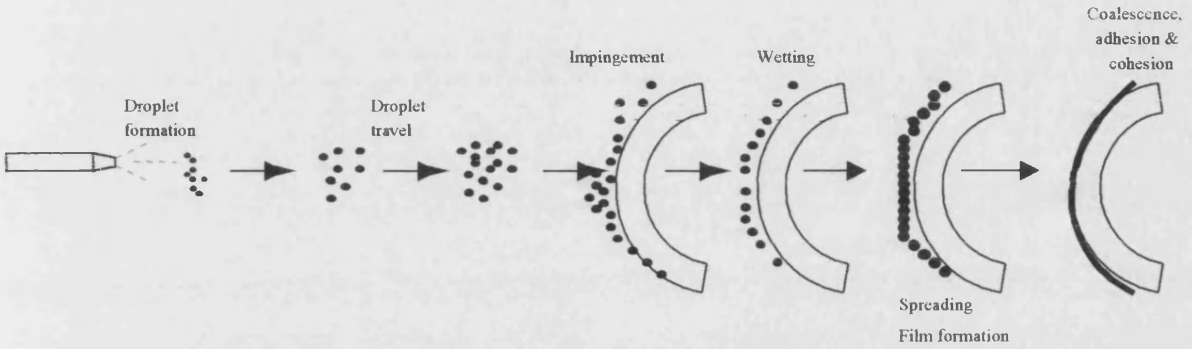


Figure 2.3 *Schematic representation of the stages in spray film coating (Cole 1995).*

There are many different methods of atomising solutions. They all tend to produce a distribution of droplet sizes. These include the following:

◊ Ultrasonic atomisation

◊ Hydraulic (airless) atomisation

◊ Pneumatic atomisation

◊ *Ultrasonic atomisation*

In Ultrasonic atomisation the fluid is subjected to intensely high frequency vibrations. This technique is not used for tablet, granule or micro-particle film coating. The lack of usage appears to be associated with difficulties in coping with the flow rates required for either organic or aqueous film coating. Furthermore the droplets do not possess sufficient momentum and the nozzle used in this technique tends to foul easily.

◊ *Hydraulic (airless) atomisation*

In hydraulic atomisation, the droplets are produced by forcing a liquid under high pressure through a small orifice. The form of the resulting liquid can be varied by changing the pressure used, or by altering the direction of flow into the orifice or by the use of different nozzles. Hydraulic atomisation is a system of choice when organic solvents are used to dissolve the film-forming polymer, since premature droplet drying is inhibited as air is not used to produce and shape the spray. Hence this technique is acceptable with highly volatile organic solvent borne film coating, but when water is used a poor quality coating is produced.

◊ *Pneumatic atomisation*

This is a method of choice for an aqueous film coating. The energy for atomisation is derived from a high-speed air stream which impinges on a jet of the solution to be atomised. In order to produce a droplet this stream has to accelerate the liquid so that it becomes unstable and also provides the energy to overcome the viscous and surface tension forces that resist the droplet formation. The droplet formed, is propelled by the expanding stream of atomising air towards the tablet core surface.

2.6.2. Film Properties

An ideal film coating should have the following attribute;

⇒ stability in solvent for coating preparation

⇒ capacity to produce an elegant coating

⇒ stability in the presence of heat, light, moisture and air

⇒ non-toxic and no pharmacological activity

⇒ resistant to cracking, breaking i.e. when film is tested for *tensile strength* it must be elastic enough to mould around a tablet without the above

⇒ no bridging or filling of the debossed tablet surfaces on film formation. Ease of printing on high speed equipment.

There are two different types of film coatings; *non-aqueous* and *aqueous* film coating. The difference only lies with the solvent used in the composition. For example if chlorinated or non-chlorinated hydrocarbon based solvent is used then it will be referred to as non-aqueous coating and where water is used as the solvent of choice it is called an aqueous film coating.

2.6.3 Non-aqueous/Organic Film Coating

Some of the typical examples of this type of film coating formulations are shown in example 1 and 2:

Example 1;

HPMC 5cP	03.20 %w/w
Ethyl cellulose 10cP	00.80 %w/w
Diethyl phthalate	00.50 %w/w
Methylene Chloride	56.75 %w/w
Methanol	33.75 %w/w
Colour Pigment dispersion (40%)	05.00 %w/w
Total solids 6% (2 polymer: 1 pigment).	

Example 2;

HPMC 5cP	05.30 %w/w
Methylene Chloride	56.10 %w/w
Ethanol	32.10 %w/w
Colour Pigment dispersion (40% solids)	06.50 %w/w
Total solids 8% (2 polymer: 1 pigment).	

The above two compositions are suitable for spraying with *airless spray* equipment.

2.6.4 Aqueous /Waterborne Film Coating

There is a growing trend towards developing aqueous film coatings because;

- ✧ the cost of organic solvent has escalated
- ✧ a number of regulatory authorities have banned some chlorinated hydrocarbons in an attempt to prevent environmental pollution
- ✧ flame proof equipment is not required, which eliminates some of the issue of a hazardous working environment.

Below are some examples of typical aqueous film coating compositions;

Example 3;

HPMC 15cP	05.00 %w/w
Colour Pigment Dispersion (30% solids)	08.30 %w/w
Plasticiser	00.50 %w/w
Purified Water	86.20 %w/w

Total solids 7.5 % (2 polymer: 1 pigment).

Example 4;

HPMC 15cP	10.00 %w/w
Colour Pigment Dispersion (30% solids)	16.60 %w/w
Plasticiser	01.00 %w/w
Purified Water	72.40 %w/w

Total solids 15 % (2 polymer: 1 pigment).

N.B. For aqueous coatings pneumatic atomisation is used.

2.6.5 Film Coating Problems

The main processing disadvantage of organic solvent borne coatings are those concerned with flame and explosion and patient compliance. Compared to organic techniques, aqueous film coating methods have received a great deal of practical attention in recent years. However the processing problems associated with aqueous film coating is the quantity of water that has to be evaporated in the process. The excess water causes degradation of the active drug if not eliminated properly. The processing time is usually longer than the organic spray coating but the procedure is still many times faster than sugar coating. It should be mentioned that in general airborne sprays are more suited to aqueous coating as they provide finer more controlled spray cone than the airless systems. This is opposite to organic solvent process.

2.7 *Future of Tablet Coating*

The presence of either organic or aqueous solvent affects the properties of the coatings on the tablet. Alternative solvents are required to minimise the usage of volatile organic solvents, for example, a *solvent-free* coating needs to be developed and water needs to be replaced in the aqueous film coating. In particular the residual solvents in coating and moisture penetration into tablet core have been questioned (Banker and Peck 1981) and remain an issue of concern. Elimination of these solvents from the coating system has been addressed as a means of eliminating the problems associated with solvent-based coatings. DeLange (1984) proposed powder coating using thermal plastic polymers. Powder coated cores were heated above the melting point of the polymer to form polymer melt coatings. Appelgren and Eskilson (1990) reported a continuous melt coating technique, which applied the polymer melt directly onto cores to form a coating, which was solidified on cooling. These two methods represent physical approaches to achieve solvent-free coatings. The coating materials do not undergo chemical reaction, such as crosslinking, and their chemical structures are not altered after coating. However, high temperatures are usually applied to melt the polymers. In contrast supercritical fluid based coatings may provide a new approach for solubilising the polymer before coating. The supercritical carbon dioxide can be used at temperatures above 31°C to solubilise the polymer without degrading it as is the case in melt coating.

3. Literature Review II - Supercritical Fluids

3.1 Introduction

A supercritical fluid is a physical state in addition to solid, liquid and gas. All these states of matter arise from variations of temperature and pressure. The relationship between different states is best illustrated in a phase diagram for a pure substance shown in fig 3.1.

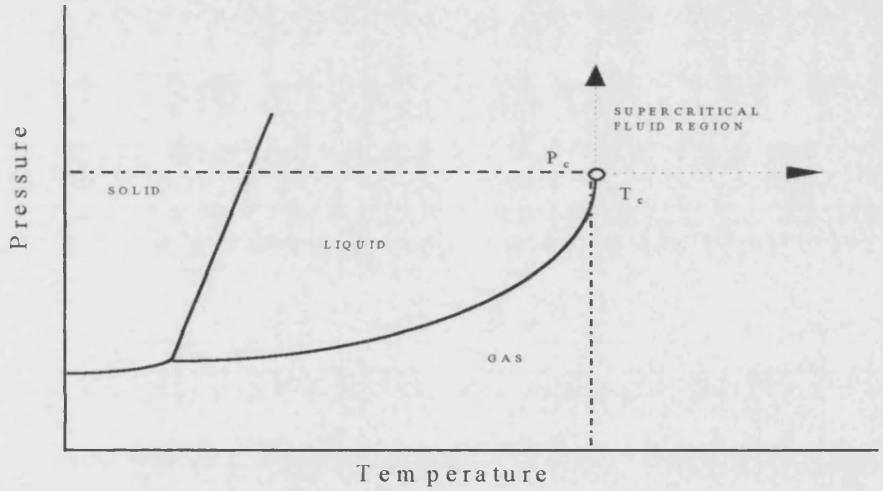


Figure.3.1 *Pressure-temperature diagram for a pure component (Atkins 1990).*

The figure 3.1 shows how subjecting a solid to heat results in melting to form a liquid and then at some point a gas. The transition points are the melting or freezing and boiling points respectively. Applying pressure either raises or depresses (depending on whether a solid occupies more or less space than a liquid) the freezing point and elevates the boiling point. If sufficient pressure is applied it becomes possible to realise a supercritical state with liquid-like densities at temperatures greater than the boiling point (Smith 1988). The

substance exists as a supercritical fluid above the critical parameters, which are defined as the critical temperature, T_c and the critical pressure, P_c. The T_c is the temperature above which liquefaction can not be brought about by altering the pressure alone. The P_c is the pressure under which a substance may exist in equilibrium with the liquid at the T_c (Weast 1968) and above which it exists as a supercritical fluid. Carbon dioxide, CO_2 is by far the most commonly used SCF for it has low critical parameters, rendering it applicable to heat labile compounds.

3.2 Historical Perspective

The root of supercritical fluid phenomenon can be traced back to Dr Andrews. In his famous Bakerian Lecture to Royal Society in 1869 he highlighted one very important parameter which he termed as the *critical point* (Andrews 1875). The critical point signified the critical pressure and temperature at which the liquid phase terminated and the gas phase began.

Hannay and Hogarth (1880) took up the challenge of analysing the state of fluids at their critical point, the critical point in this case being the temperature. Hannay *et al* found that when pressure was applied above the critical temperature the solvent properties of some fluids e.g. alcohols increased. They observed that changes in pressure caused several inorganic salts (e.g. cobalt chloride, potassium iodide, potassium bromide) to dissolve or precipitate from ethanol at a temperature above the critical temperature of ethanol (T_c = 234°C). They found that increasing pressure on the system caused the salts to dissolve and that decreasing the pressure caused the dissolved material to nucleate and precipitate "as a

snow". They proved that the power of solubilising does not exclusively belong to liquids but also to supercritical fluids. The pressure-dependant dissolving power of a supercritical fluid is not limited to inorganic salt solutes - it is a general phenomenon exhibited by all supercritical solvent-solute pairs.

After the first reports by Hannay and Hogarth a number of researchers reported solubility phenomenon with a variety of supercritical solvents. Supercritical solvents such as carbon dioxide and nitrogen oxide were used. Villard (1898) contacted supercritical oxygen, air and hydrogen with metallic salts of bromine. In this instance Villard placed a drop of liquid bromine at the bottom of a narrow glass tube and passed compressed oxygen (200 atmosphere) by the upper end. He observed the colour become much more intense; diffusion gradually taking place and colouration filling the whole tube interior. He concluded that changes in colour intensity were an indication that solubility was changing with pressure. He conducted his experiments between 4-300 atmospheres and came to realise that the *solvent power* of supercritical fluids was related to its *density*. Villard reported air to have behaved in a similar manner to oxygen, however the colour intensity was not so strong. Hydrogen was one of the most difficult to liquefy and only demonstrated a feeble solvating power.

There was little progress, if any, between 1898 and the 1940s. Deipen and Scheffer (1948) reported in their paper that the solubility of naphthalene in supercritical ethylene was high. They calculated the solubility of naphthalene in ethylene and indicated that the sudden increase in solubility only occurred near the critical point.

Further attempts to interpret the solubility data were made; in this case solubility of phenanthrene was measured in a few dense gases/supercritical fluids. Robin and Vodar (1953) recognised high solubility rates in supercritical fluids using an equation of state limited to the *2nd virial coefficient*. They also realised that expression such as Poynting's formula, Dalton's rule and Van der Waals equation were not valid here for describing this system.

Exploratory work on supercritical carbon dioxide, $scCO_2$, began for the first time in 1962. Tsekhanskaya *et al* (1962) measured solubility of diphenylamine and naphthalene in $scCO_2$ as part of their work to investigate rates of diffusion in dense gases. They used a similar method to Robin *et al* for solubility calculations and found the solubilities to be in good agreement at higher pressure where carbon dioxide's, CO_2, density was greater than the critical values. At lower pressures, no correlation was seen - in fact the solubility curve could not be reproduced in this region.

Tsekhanskaya *et al* (1964) re-addressed this problem and discovered that the problem lay with the apparatus he was using. The pressure in the equilibrium cell was not being measured directly. It was discovered that dissolving a solute in $scCO_2$ lowered the pressure thereby the pressure in the cell at equilibrium was lower than expected. Tsekhanskaya repeated the earlier experiments using continuous gas admission to prevent pressure drop in the equilibrium cell. The solubility of naphthalene was re-measured and was in-line with Diepen & Scheffer (1948) with a less significant error of 2-4%.

After the initial familiarity with supercritical fluid behaviour, researchers began to look at ways of utilising supercritical state. Supercritical fluids are primarily seen as solvents for

extracting, or media for chemical reactions, namely, chromatography and recrystallisation. The notion of extracting was utilised as early as 1936 by Wilson *et al*, when they used supercritical propane to remove asphalt from oil. However the first commercial process to use supercritical fluids was coffee decaffeination (Zosel, 1974) which involved circulating wet supercritical carbon dioxide through a bed of moistened green coffee beans. The carbon dioxide containing the coffee was passed through a water pool where the coffee was extracted. This process removed half of the caffeine from the coffee beans. Roselius *et al.* (1974) improved this process by using dry supercritical carbon dioxide to extract coffee oil from roasted beans. A coffee extract was produced from decaffeinated beans, which were mixed with coffee oil to give an acceptable coffee flavour. Moyler lists over 80 varieties of seeds, roots, leaves, flowers, fruits and barks that have been successfully extracted with supercritical carbon dioxide and supercritical carbon dioxide based extracts of celery, ginger, rosemary and vanilla are currently available commercially (Moyler 1993). Later, edible oils and flavours were extracted from foods, examples include; oils from Soya beans, Sunflower seeds and fish (Friedrich 1984). Previously oils used to be extracted using traditional *volatile organic solvents* (VOC), such as hexane and heptane. The disadvantage with these was that organic solvent processes tended to run at higher temperatures, which ruined the quality of the extracts, especially delicate flavours. Furthermore the organic solvents were toxic and a health and safety hazard. Now because of the environmental pressures supercritical fluids are seen as an alternative solvent for extracting instead. Supercritical fluids have the added advantage where by they do not need to be run at high temperatures and are more energy efficient and retain full flavour of the extract. Other commercial uses of supercritical fluid extraction method include; oil upgrading and asphalting, removing organics from water, regenerating activated carbon dioxide, and finally extracting components from coal. Apart from extraction supercritical

fluids are being used in chromatography and recrystallisation among some of the other uses of modern day.

3.3 Supercritical Fluid Extraction (SFE) Process

Zosel (1963) introduced the true potential of supercritical fluids as an extraction media. After this, there was some developmental work in the field of process engineering particularly in the removal of lighter products from the residue of commercially distilled crude oil (McHugh *et al* 1986, Nicoloan 1985). After the potential of SFE had been demonstrated there was a steady growth in the chemical engineering field. One of the most well known applications is the decaffeination of coffee which is now carried out on a large scale (Rizvi, 1986). During the 80's and 90's applications have been geared towards optimising known techniques (see table 3.1).

SFE Process	Type of Supercritical fluid	Comments
Decaffeination of coffee	Carbon dioxide, CO_2	SFE by HPLC method, (Kumar *et al* 1988)
Alcohol removal from Jojoba oil	CO_2	SFE by capillary supercritical fluids chromatography, (King 1990)
Alkanes from Basil and euclaptus leaves	CO_2	SFE by Gas chromatography/Mass Spectroscopy.

Table 3.1 *SFE Processes.*

SFE can be used in *static* and *dynamic* processes. In static SFE the extraction vessel containing the sample is pressurised to the required pressure and then left for a length of time while extraction takes place. In dynamic SFE, there is a continuous flow of fluid over

a sample and collection of the extract in a suitable solvent or on a solid trap. The extraction may also be either off-line or on-line. In off-line SFE extracts are collected and analysed later whereas in on-line SFE there is direct coupling of the SFE instrument to the analytical instrument.

In SFE the rate and extent of extraction is of prime importance. Three factors govern the extraction process (Clifford 1993);

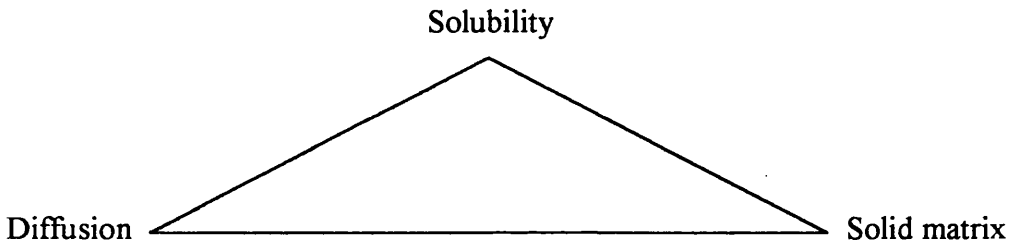


***Figure 3.2** Showing the SFE Principle*

The figure 3.2 can be explained in terms of how the solute must be sufficiently soluble in supercritical fluids. This is governed by the volatility of the solute and the solvating effect of supercritical fluids. The second factor in influencing the recovery is the diffusion of the solute out of the matrix. The third factor is the effect of the matrix. During an extraction some of the solute may be 'non-extractable' because it is locked onto the structure of the matrix or strongly adsorbed on its surface.

3.4 Supercritical fluid Chromatography (SFC) Process

The reports of using supercritical fluids as the chromatographic mobile phase can be traced back to Klesper et al (1962). The technique was then known as high pressure gas chromatography. In the 80's supercritical fluid chromatography, SFC gathered momentum as it offered higher speed separation with higher resolution (Springston *et al* 1984, Harata *et al* 1984) in comparison to *High Performance Liquid Chromatography (HPLC)*. A Chromatography system comprises of a stationary phase, mobile phase and a detector.

The most popular mobile phase for SFC is carbon dioxide. It is compatible with a wide range of detectors. One of the other advantages of SFC is that nearly all Gas (GC) and Liquid Chromatography (HPLC) detectors can be used (Yang 1989). The detectors most commonly used are the ultra violet absorbance or the flame ionisation detectors. The latter is not suitable for organic mobile phase.

SFC is widely used in the pharmaceutical industry where the most commonly used mobile phase has been carbon dioxide with a *co-solvent* like methanol. Selected applications of SFC are shown in table 3.2.

Stationary phase columns used for GC and HPLC are also amenable to the SFC technique. Typically these columns are packed with silica, alumina or derivatised silica particles.

Analyte	Column	Fluid	Condition
Sulphonamides (Berry *et al* 1986)	packed colmun, silica gel, 5µm, 100mm x 4.6mm(i.d).	CO_2 + Methanol.+ Acetonitrile	UV at 270nm and MS detection.
Non-Steroidal Anti-inflammatory Drugs (NSAID), e.g. Ibuprofen + Phenylbutazone. (Jagota & Stewart 1992).	Capillary Column 10m x 50µm(i.d)	CO_2	1-3ml/min 200 bar, 150°C, MS detection.
Cephalosporins (antibiotic) (Lane 1988)	Column spherisorb, 5µm 100mmx 4.6mm i.d.	CO_2 + 4.5%Methanol	UV and MS detection

Table 3.2 *Selected applications of supercritical fluid chromatography.*

3.5 Other applications of supercritical fluids

3.5.1 Preparation of controlled release drugs

Supercritical fluids have been used in the investigation of controlled release drugs. Controlled release provides sustained release of drugs in the human body. Of the most common methods for the controlled release of drugs is the use of drug loaded *polymer microspheres* and *protein microparticles*. The polymer-drug microspheres are produced by *rapid expansion of a supercritical solution*, RESS. The protein microparticles are also produced from supercritical fluids but by a method known as *gas anti-solvent crystalline solution* (GAS crystallisation). Both RESS and GAS crystallisation are described briefly in section 3.6.1 1and 3.6.1.2. In this study, by Tom and Debenedetti (1993) RESS and GAS crystallisation have been used to produce biodegradable polymer-drug microspheres

(<50 μm) and micron sized protein (< 5 μm) particles respectively. The advantages that RESS and GAS crystallisation have over conventional methods of polymer-drug microsphere formation and particle reduction are numerous. Pharmaceuticals are often prone to degradation or denaturation by heat or oxygen. Their processing often requires mild or inert conditions. Conventional sized reduction methods such as milling and grinding can adversely affect the crystallinity and chemical stability of the pharmaceuticals (Otsuka 1990). The use of low-critical-temperature solvents allows processing at mild temperature and can lead to the formation of very fine and monodispersed powders.

3.5.1.1 Rapid Expansion Supercritical Solution, RESS

RESS is one of the first processes to be used for pharmaceutical particle reduction (Mohamed 1989). RESS has also been applied to ceramic and polymeric processing. In RESS, a non-volatile solute is dissolved in a supercritical fluid. Precipitation of the solute is triggered by reducing the solvent's density and therefore its solvating capacity (Kumar and Johnston 1988), through rapid expansion. The material of interest is dissolve at high pressure (200 bar), exploiting the supercritical fluid's solvent power, and then precipitated it mechanically thus exploiting the solvent's high compressibility.

The use of RESS as a means of producing polymer-drug microshperes has the potential for eliminating some of the disadvantages of conventional methods. Current techniques for producing drug microshperes involve dissolution of the polymer and drug in a common organic solvents. Microspheres are formed from such a solution either by the addition of an aqueous solution (with dispersing agent) which acts as an antisolvent, or by evaporation of the solvent (Rosen *et al*, 1988). A similar technique, spray drying, involves spraying a

solution of polymer and drug into a hot gas to remove the solvent. Microspheres can also be formed by melt pressing the polymer and the drug, and subsequent grinding. These conventional techniques require the removal of surfactants and organic solvents, and involves the use of high temperatures (spray drying and melt pressing). In manufacturing of microparticles intended for *in vivo* use, the removal of residual surfactants and solvents is a particularly important requirement. However, removal of these residues often requires prolonged vacuum or exposure to high temperatures. In contrast RESS does not involve surfactants, organic solvents or high temperatures (if a low-critical-temperature solvent is used), and it yields a solvent-free product (the supercritical solvent is a dilute gas after expansion) in a single processing step.

3.5.1.2 Gas Anti-Solvent Crystallisation, GAS

A more recent application of supercritical fluids to particle formation is gas anti-solvent crystallisation (Gallagher *et al*, 1989 and 1991). In GAS crystallisation a supercritical fluid is used as an anti-solvent that causes crystallisation of solids. The solids are dissolved in a liquid, and a supercritical fluid (having low solvent power with respect to the solids, but miscible with the liquid) is added to precipitate the solids. The size distribution of the precipitate depends on the rate of addition of the supercritical fluid. The dissolution of the supercritical fluid at 90 bar in liquids is often accompanied by a large volume expansion and consequently, a reduction in the liquid's solvent power. Rapid addition of a supercritical fluid results in a sudden reduction in the liquid's density, a sharp rise in the supersaturation within the mixture and the consequent formation of small and uniform particles. GAS is useful for the processing of solids which are difficult to solubilise in

liquids or sensitive to mechanical handling. Pharmaceutical compounds such as polymers and proteins fall into this category.

There are several problems associated with conventional size reduction methods for proteins and this makes GAS crystallisation an attractive alternative. Processes such as spray drying, milling, grinding, lyophilisation and sieving either produce particles whose size is often not small enough for incorporation into controlled release microparticle or have features, which can inactivate the proteins. Spray drying can reduce particles to less than 5μm, but exposure to heat and air in the process can deactivate proteins. Sieving of lyophilised proteins can reduce particles only to 70μm. Milling and grinding can produce particles of less than 5μm, but can not denature protein compounds. Milling and grinding also require large quantities of material which makes processing of highly potent and expensive enzymes impractical (Gombotz 1990). Finally GAS crystallisation has the potential of separating the liquid solvent from the products in a single-step process.

3.5.2 Spray Painting

Traditionally car manufacturers have been using organic solvent for applying paint on the body since these solvents have the capacity to lower the viscosity of the paint so that it can be atomised as it is sprayed from the gun. Airless spray gun is used to apply a mixture of paint and solvent; the solvent escapes by evaporation. Busby *et al.* (1990) have patented a method of replacing the volatile organic solvents with supercritical carbon dioxide. The spray characteristics have been found to be superior to that of the conventional airless spray. This method has been tested successfully with a wide range of paints. A disadvantage is that not all the organic solvents used can be replaced by supercritical

carbon dioxide, however, a 70% reduction in VOC emission is claimed by Busby *et al* (1990).

3.6 Environmental Benefits of scCO2

Supercritical carbon dioxide is emerging as a 'green' solvent in variety of industrial processes as it offers an environmentally friendly alternative to variety of organic solvents. Supercritical carbon dioxide attracts most of the interest because it is not toxic or flammable, and unlike chlorofluorocarbons does not threaten the ozone layer. Chlorofluorocarbon are still used in some polymer manufacturing (Black 1996). These chlorofluorocarbons are classed as volatile organic compounds that are detrimental to the environment in many ways. For example, when released into the atmosphere, they facilitate production of ozone (O_3), a compound which is desirable in the stratosphere to block ultraviolet rays, but which is toxic at ground level. Short-term exposure to ozone contributes to eye, nose, and throat irritation. It can also lead to congenital birth defects (Suess *et al* 1985).

Official authorities such as the federal, state and local regulation have become increasingly stringent on the VOC emissions. Recently, the Clean Air Act (CAA) regulations have been extended to include the emission of individual VOCs that are classified as hazardous air pollutants (HAPs). This includes most common coating solvents, particularly those of high volatility such as methyl ethyl ketone, methanol, hexane, toluene and xylene (Donohue *et al* 1996). Because of this great need to reduce VOC emissions, considerable

effort is being put in to developing new ways to coat tablets with much less organic solvent.

3.7 Future of $scCO_2$ in Pharmaceutical Coatings

Existing tablet coating solvents solubilise the polymer and produce high quality film coatings, however they are very expensive and environmentally unfriendly, unlike supercritical carbon dioxide. $scCO_2$ is very cheap and less harmful to the atmosphere. A carefully worked out rig design can utilise carbon dioxide for solubilisation of coating polymer and the production of a polymeric film.

Preliminary studies into the solubility of tablet coating polymers have been done (Broadbent 1995) here in the School of Chemical Engineering. The results showed very low solubility of the polymer in pure supercritical carbon dioxide. The lesson from this is to make use of a small percentage of *co-solvents* such as ethanol, methanol or methylene chloride. Ekart (1993) suggests that a presence of 2% co-solvent such as ethanol can increase the solubility by more than 2 orders of magnitude. It appears that traditionally organically based tablet coatings can be upgraded by using a co-solvent mixture which is rich in supercritical carbon dioxide and considerably less toxic to the operators in the pharmaceutical industry and environmentally friendlier than its predecessor. In commercial application this new technique could reduce VOC emission in this area by up to 70% and can significantly eliminate hazardous air pollutants (Busby *et al* 1991).

4. Rig Design

4.1 Aim

The initial step was to design and build a rig to investigate solubility of polymers in $scCO_2$. The secondary stage was to observe the solvent power of the supercritical carbon dioxide at various temperatures and pressures and determine the solubility of the test polymer at these conditions. The tertiary stage involved modifying the solubility rig to accommodate a co-solvent system and determine solubility in this system, in order to draw comparison between pure supercritical carbon dioxide and a $scCO_2$-Methylene chloride system. Finally further modifications were made to the cold trap to collect a polymeric film.

4.2 Overall Design Issues

The solubility rig was constructed bearing in mind a number of design constraints. The overall principle behind a rig of this type is to compress and pump liquid carbon dioxide to a high pressure, subject it to temperature up to 200°C thus taking it above its critical point and hence to supercritical state and bringing supercritical carbon dioxide into contact with a polymer. The solubility rig was designed with the following issues in mind; required pressure, temperature, residence time and safety.

4.2.1 Pressure issue

The solubility rig was designed to operate at pressures of between 70 and 650 bar. Relief valves were incorporated to prevent the build up of the excess pressure at any one point. Two relief valves were used in this rig; one upstream just before the pump inlet and one further downstream prior to entering the equilibrium cell to prevent over pressurisation at these points owing to blockages. By-pass systems were included next to these relief valves to relieve excess pressure. High-pressure stainless steel tubing with a pressure rating of 1350bar at 200°C was selected for this research work. Pressure transducers were installed before after the equilibrium cell and these were linked to a display unit for constant monitoring of pressure in the equilibrium cell.

4.2.2 Temperature issue

The reaction cell was housed in a temperature-controlled oven to maintain the test temperature. The oven maintained the set temperature to within ± 0.1°C; it was also fitted with an independent thermostat that was set to operate should the temperature exceed the set point by 20°C. To measure the temperature before and after the reaction cell, two temperature transducers were incorporated in the rig and were housed in the oven. An analogue type display unit was connected to the two transducers, so that there was a constant monitoring of the temperature of the rig within the oven.

4.2.3 Residence time.

In order to reach equilibrium the residence time of the carbon dioxide must be as high as possible. It is well known that equilibrium is reached quickly due to high diffusivity of carbon dioxide (Kurnik *et al.*, 1981). To allow the supercritical carbon dioxide to equilibrate Broadbent (1995) conducted a series of experiments at the same temperature and pressure with different flow rates (hence residence time) with naphthalene as the solute. He found that a flow rate of 2L/Min was the optimum flow rate for this system.

4.2.4 Tunnelling effect

The equilibrium cell was packed with a mixture of the test polymer and glass ballotini (1.5mm diameter). This was to prevent carbon dioxide from channelling through the centre and thus creating a by-pass through the packed bed of test polymer with minimum contact. Initial studies using polymer without ballotini showed evidence of channelling, following the introduction of ballotini no channelling was observed.

4.2.5 Safety

From a safety consideration all the high-pressure tubing were designed to go in the oven. The reaction cell was set-up in the oven to minimise the risk of damage in the event of a sudden pressure release. Oven gloves were used when removing the reaction cell when warm. Protective shoes were worn all the time. Warning labels were clearly displayed when the solubility rig was running. Goggles were worn during the experiment. Electrical heat tracing along the length of tubing emerging from the oven was covered with a jacket

of insulation material. This was to prevent the operator or technician from burning their hands.

4.2.6 Blockages

To prevent the flow back occurring of polymer-$scCO_2$ solution, non-return valves were incorporated at key points, such as after the carbon dioxide cylinder and after the drying column. This ensured that no back flow would occur during the shut down procedure, following an experiment.

4.3 Materials for the construction of the solubility rig (see figure 4.4)

4.3.1 Carbon Dioxide

The carbon dioxide was supplied by BOC Limited, Surrey, U.K. It complied with the British Standard, BS4105. It was 99.8% pure in liquid withdrawal cylinder pressure rated to 60 bar at 20°C. A regulator was not required as the carbon dioxide was pumped to a higher pressure than the cylinder pressure.

4.3.2 Drying Column

An oval shaped vessel (Swagelok Company, Ohio, U.S.A.), with an internal volume of 3785 cm^3 was used as a drying column. This was packed with 5Å molecular sieve, as

adsorbent (Aldrich Chemical Company, Poole, U.K). The adsorbent was regenerated regularly by heating to 300°C in the presence of nitrogen.

4.3.3 Filter 2μm.

The filter was a stainless steel disc, Nupro make supplied by Swagelok Company, Ohio, USA. This was installed between the drying column and the entrance to Teledyne pump to prevent any flow of dust or molecular sieves into the pump head.

4.3.4 Cooling System.

This was used to maintain carbon dioxide liquid phase, since carbon dioxide had a tendency to vaporise in the drying column and in the pump head [referring to the Teledyne reciprocating pump] at room temperature. A flexible silicone rubber tubing was wrapped round the drying column and the pump head to circulate antifreeze solution (Ethanediol GPR grade, BDH, Poole, UK). An immersion cooler (Haake, Cambridge, U.K.) was used in conjunction with a water bath (Haake, Berlin, Germany) to cool down the antifreeze solution to –5°C. A circulating pump (RS Components, Corby, UK.) was used to pump the cold antifreeze based solution (3:2 dilution) round the drying column and the pump head.

4.3.5 Relief Valves (RV1)

A variable relief valve (RV1) from Swagelok Company, Ohio, U.S.A was used to protect the low pressure side of the rig from over pressurising. This was set to lift at 90 bar, 30 bar

higher than the operating pressure of this part of the rig. Teflon Seals within this valve were checked regularly as they often cracked owing to extremely cold carbon dioxide

4.3.6 Teledyne Pump.

A compressed air driven pump (Teledyne, Ohio, U.S.A.) as in figure 4.1 was used to supply liquid carbon dioxide at experimental pressures up to 650 bar. This pump had a mechanical separation between the head and the air driven side to prevent contamination of the carbon dioxide with oil. The pressure of carbon dioxide was adjusted by manipulating the rate of compressed air at inlet using a regulator. This pump magnified the pressure by 150 times (1:150 ratio).

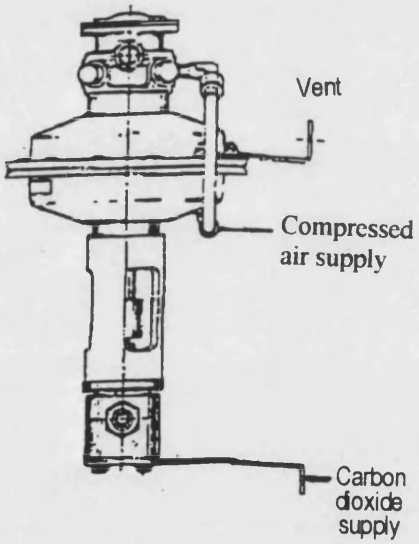


Figure 4.1. *Diagrammatic representation of the Teledyne Pump.*

4.3.7 Tubing and Fittings

In selecting suitable tubing for this work, the following variables were considered:

- Tubing material
- Tubing wall thickness
- Tubing surface finish
- Tubing hardness.

After careful study, tubing of 316 stainless steel with 0.08" wall thickness, 1/4" outside diameter, and hardness of Rb 80 was purchased from Southampton Tube Sales, Southampton, U.K. The tubing had a pressure rating in excess of 20,000 psi (1380 bar), at 200°C. The fittings used were either from the Sno-Trik range (Swagelok Company, Ohio, U.S.A.) or from Autoclave Engineers (Pennsylvania, U.S.A.) and had a pressure rating of 60,000 psi (4140 bar).

4.3.7.1 Fitting Safety

Tubing was chosen over pipe for easy installation and removal and ease of maintenance. The stainless steel tubing chosen has hardness of Rb 80, which is suitable with Swagelok fittings of stainless steel that are of Rb 90 hardness. Swagelok recommend that softer tubing is used than its fittings so that fittings can mould into the surface of the tube to ensure that a leak-free connection is made. Brass fittings were not considered, as these fittings would not create a seal due to incompatible metals neither was the option of welded tubes considered, because of the high pressures that were intended to be used.

When tubes were bent, enough straight bit was left and support was used around valve fittings to secure the rig.

4.3.8 Pre-Heat Coil

This comprised of a 3m length of high-pressure rated tubing to form a coil 200mm in diameter and was connected to the solubility rig using Sno-Trik unions. The purpose of this was to increase the residence time of the supercritical carbon dioxide to allow it equilibrate to the test pressure and temperature.

4.3.9 Relief Valve (RV2)

This relief valve (see Appendix 2) was supplied by Autoclave Engineers, Pennsylvania, U.S.A. It was incorporated into the high-pressure side to prevent over pressurisation. It was set to lift at 10,000 psi (690 bar). This vented to the outside via a 28mm diameter copper line.

4.3.10 Equilibrium Cell

The equilibrium cell (see Appendix 1) was designed in-house and constructed from 316 stainless steel. This was a cylindrical vessel, of internal length 35cm, diameter 1.8cm and internal volume 89cm^3. Details of the design are given in appendix 1. Later very fine mesh was welded on to the end connectors to prevent ballotini from flowing back.

4.3.11 High-Pressure Valves

All the high pressure valves (HV1, HV2 and HV3) used were manufactured by Autoclave Engineers, Pennsylvania, U.S.A. These had a pressure rating of 30,000 psi (2070 bar). A micrometering valve (TV1) from the same company was used as a throttle to allow accurate flow of carbon dioxide.

4.3.12 Oven

Oven was used to house the equilibrium cell together with the pre-heat coil in order to control the temperature and secondarily to protect the operator. It also facilitated studies at a range of temperatures. The oven was made to BS2648 (Gallenkamp Leicester, U.K.). A thermostat maintained the set point temperature to within ± 0.1°C. In order to protect the equilibrium cell from over heating, the oven was also equipped with an independent thermostat, which was set to operate should the temperature exceed the set point by 20°C.

4.3.13 Bypass Lines

There are two bypass lines in this rig; one on the low-pressure side and the other on the high pressure side. The function of the former is to make sure that only liquid carbon dioxide is flowing into the system. Opening of valve LV4 permits purging of the system. The latter bypass line was used to clear out any polymer trapped in the tubing leading to the cold trap. It also isolated the equilibrium cell and permitted the operator to run solvent through the high-pressure side. The valves for this were located above HV1 and below HV2 respectively.

4.3.14 Heat Tracing

An electrically heated tracing was set to the experimental temperature to insulate the length of tubing leaving the oven and the valves HV3 and TV1. This was to prevent the solute from precipitating before the throttle valve (TV1). The thermostatically controlled heat tracing equipment was made in-house. It operated in the range of 20-200°C.

4.3.15 Pressure and Temperature Display Unit

A digital display unit made in-house was connected up to pressure and temperature transducers, to give a direct reading of temperature and pressure (see figure 4.2) during an experiment. These were dual function transducers (Paine, Washington, U.S.A.) and they were incorporated before and after the equilibrium cell. They had a spiral wound strain gauge to measure the pressure, and a platinum resistance temperature device (RTD) to measure temperature.

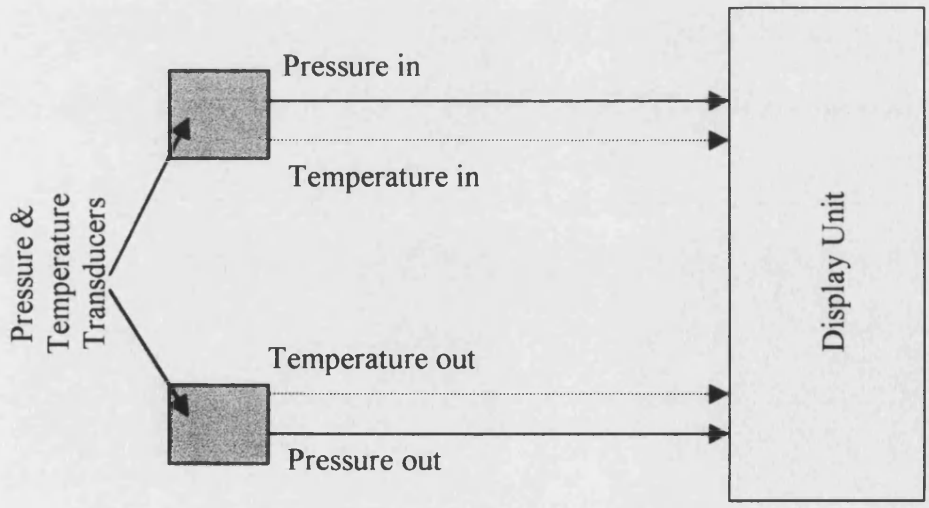


Figure 4.2 *Pressure and Temperature Monitoring Unit.*

4.3.16 Cold trap

The cold trap essentially consisted of a soda glass U-tube placed in a beaker filled with water and maintained at the required test temperature. The U-tube was made in-house from 18mm soda glass tubing, and it weighed approximately 60g. A U-tube is shown in Fig 4.3. They were designed to have a threaded joint to connect with the stainless steel tubing emerging from the throttle valve (TV1). The other end connection was a ground glass joint, which was sealed with a PTFE sleeve. A chamber was incorporated at the ground glass joint, which housed a plug of glass wool to act as a filter, to trap any particulate formed. Four U-tubes were made in house for this project.

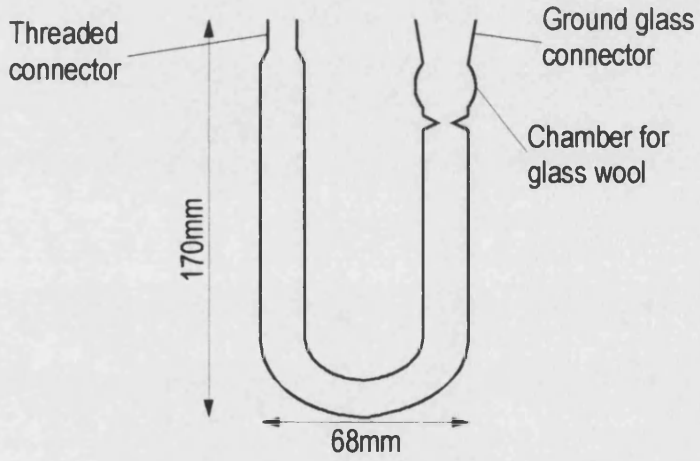


Figure 4.3 *A U-tube cold trap*

4.3.17 Gas Meter.

The volume of carbon dioxide gas used in each experiment was measured by a dry gas meter from Fisher Scientific Ltd., Leicester, U.K. Accuracy was ± 0.2 dm^3 at standard

temperature and pressure. The use of a wet gas meter was considered but they were discounted, on the grounds that they were unable to measure large volume of gas used.

4.3.18 Flow meter

This was purchased from KDG Mobrey Ltd., Slough, UK. It was an 1100 series tube, made from Borosilicate glass, calibrated for carbon dioxide and ISO9001 quality approved. It could handle flow rate from 0.5-14L/Minute and it was pressure rated to 11 bar at 100°C.

4.3.19 Important Note

A new low pressure (0-350 Bar) solubility rig was designed, constructed using 1/8" tubing and HPLC pump. It was validated with Naphthalene and worked well initially for the low pressure work. The problems encountered were linked with incompatible tubing and HPLC pump. In addition, owing to a limited budget the low pressure rig was not considered to be cost-effective to enhance the high pressure work. Due to drawbacks in the low pressure rig and that used by a previous researcher (Broadbent 1994) the latter high pressure rig was modified. This modified high pressure solubility rig is presented in figure 4.4. The Solubility rig in figure 4.4 was used for the determination of solubility in the supercritical carbon dioxide. A further modified version (see figure 4.6) of the solubility rig in Figure 4.4 was used to determine solubility of polymers in a co-solvent. The solubility rigs in figures 4.4 and 4.6 were designed and constructed from ¼" tubing of the hardness of Rb 90. The experimental and rig design chapters are based on the solubility rigs presented in figure 4.4 and 4.6.

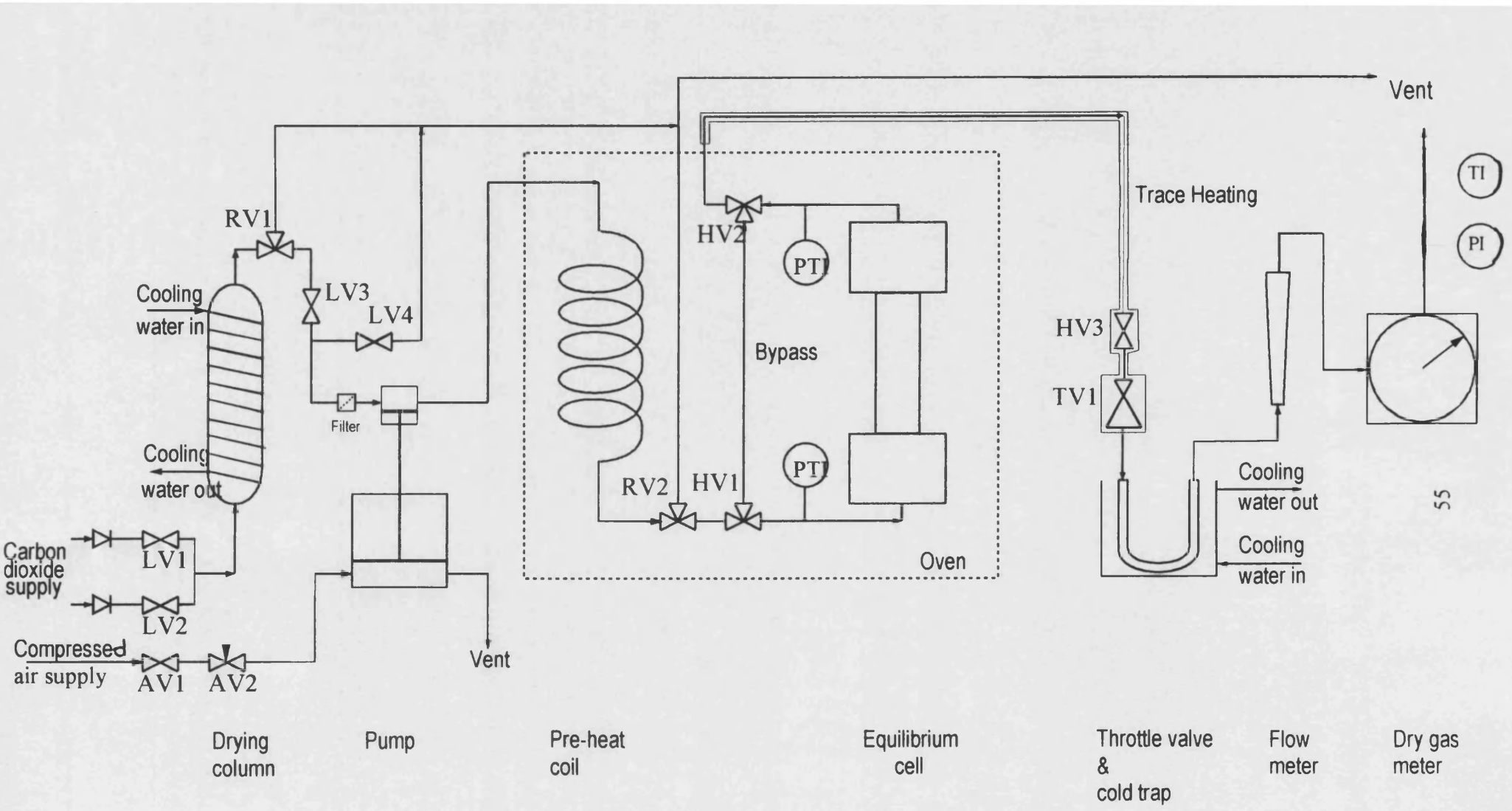


Figure 4.4. *Flow Diagram of Supercritical Solubility Rig.*

4.4 *Co-solvent Rig - Additions to the solubility rig*

Modifications were made to the solubility rig (see section 4.5.4) to accommodate an organic solvent feed in order to determine solubility in a co-solvent: Methylene chloride was the solvent of choice. A Liquid Chromatography pump (SP8810 Spectra Physics, California, USA) was donated by SmithKline Beecham Pharmaceuticals for the purpose of this research. It was chosen for its accuracy in delivering very low flow rates. This pump was only able to accurately deliver 1.25 x 10^{-4}L/Min (0.125ml/minute) successfully. Hence this was the only flow rate studied. The service was carried out by Thermo Quest Engineers, Manchester, UK. A number of tests were carried out to determine an accurate delivery volume of methylene chloride.

4.4.1 Non-return Valve.

A non-return valve was incorporated in the tubing exiting from the SP8810 pump to prevent the back flow of methylene chloride. A similar valve was incorporated just after the liquid carbon dioxide cylinder to prevent the flow back of a mixture of carbon dioxide and methylene chloride into the carbon dioxide cylinder.

4.4.2 Mobile Phase

Methylene chloride was the solvent of choice here for it is a typical solvent in organic tablet coating practices and it is Food and Drug Administration, (FDA) and British Pharmacoepia, (BP) approved. Methylene chloride was pumped from a liquid chromatography pump at the same pressure as the carbon dioxide from the cylinder

pressure. This pump was set to operate up to 50 bar delivery pressure, which was similar pressure to carbon dioxide from the cylinder. The two streams joined at a Tee-piece prior to entering the High Pressure Liquid Chromatography Pump. This mixture was compressed and heated to the test pressure and temperature respectively to determine how much the solubility improved with the addition of the co-solvent.

4.4.3 Cold Trap

The cold trap was modified to house two U-tubes. Hence two containers were set up; one to collect the polymer and the other to collect the organic solvent. The former was maintained at the test temperature for collecting any polymer and the latter was cooled to – 5°C to condense and liquefy the organic solvent and prevent its entry in to flow meter. A diagram of this arrangement is shown below in fig 4.5.

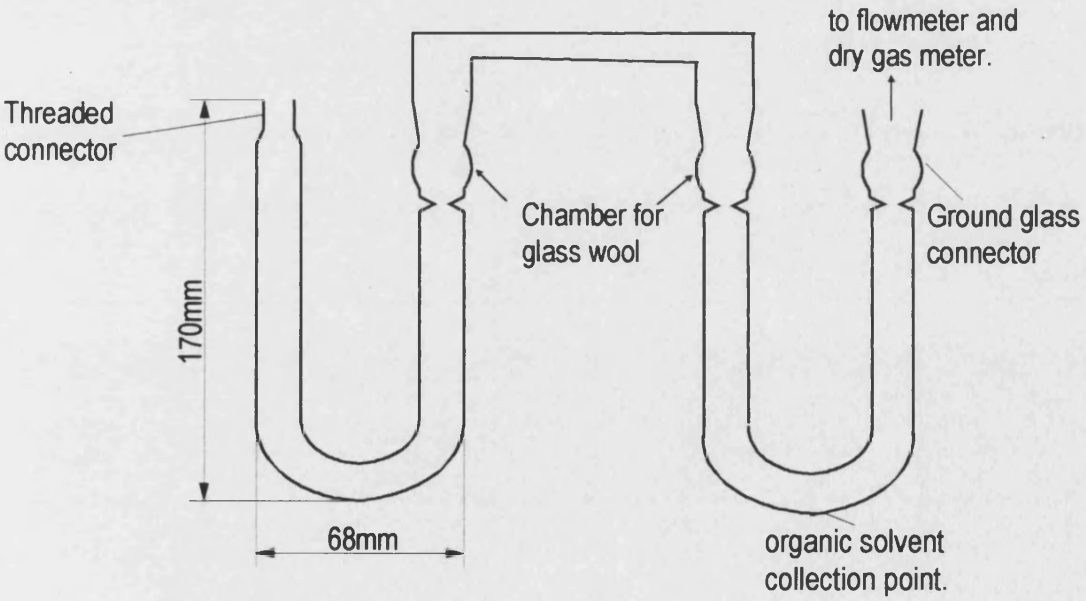


Figure 4.5 *Modified U-tube cold trap for a co-solvent study.*

This arrangement did not prove to be successful as some of the organic solvent condensed in the first U-tube. At this point it was decided to revert to the original collection system (see figure 4.3). The polymer collected was heat dried to remove condensed solvent.

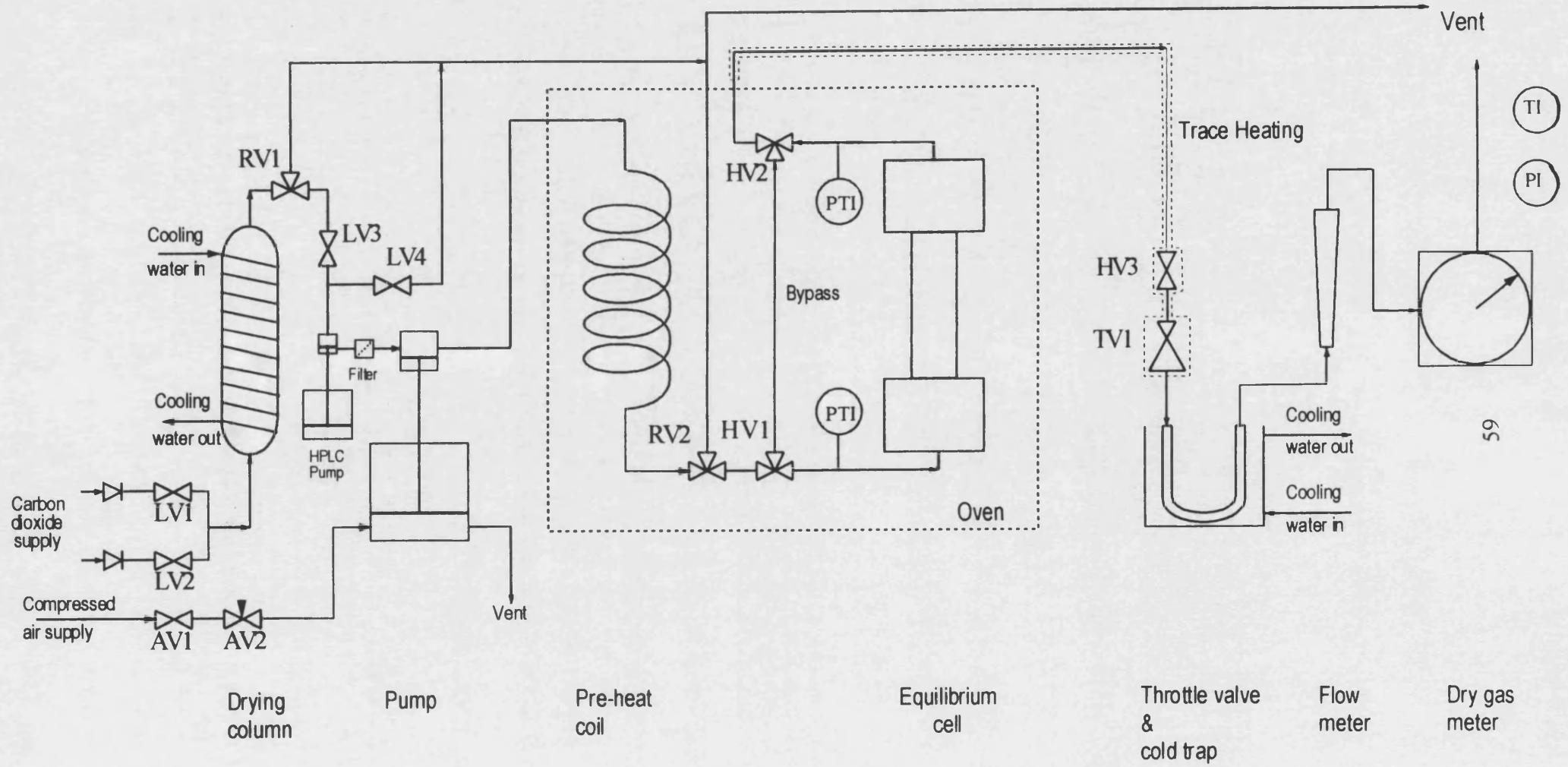


Figure 4.6. *Flow Diagram of Co-Solvent Rig.*

4.5 Film Production

Using the co-solvent rig and modification to the cold trap, it was possible to collect a polymeric film from a tablet coating polymer. The cold trap was replaced by a flat base conical flask with a side vent (see figure 4.7) that was connected to the flow meter and gas meter.

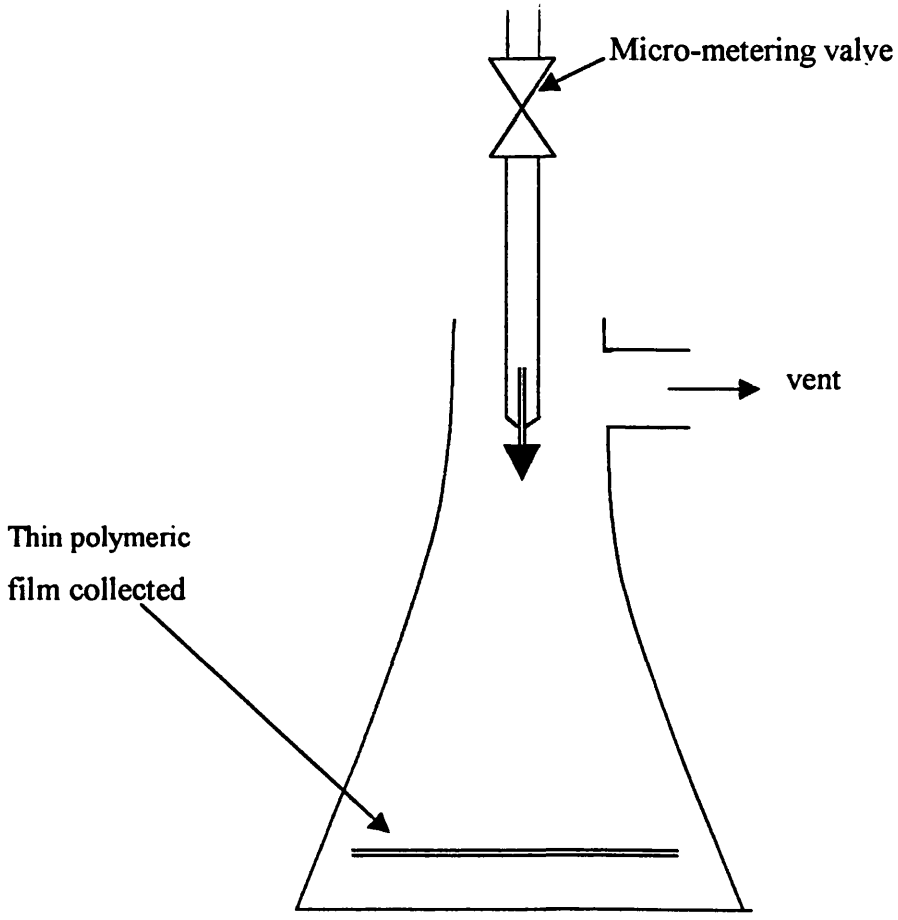


Figure 4.7 *New cold trap for the collection of a polymeric film.*

5. *Methods and Materials*

5.1 Introduction

This chapter gives details of the methods and materials used for acquiring solubility data for a range of tablet coating polymers. The solubility of polymers of pharmaceutical interest was investigated over a range of temperatures and pressures in pure *supercritical carbon dioxide* and in the *supercritical carbon dioxide - co-solvent system.* A small percentage of co solvent was used due to equipment constraints and with environmental and health considerations in mind. 2.5 % v/v of methylene chloride was used. The intention of this project was to keep the percentage of the co-solvent to a minimum.

5.2 Materials for the experimental

5.2.1 Naphthalene

Naphthalene (Mol. Wt. = 128) is manufactured by Merck Ltd, Poole, UK. It is a white crystalline powder. It is a well studied material in supercritical fluid technology and is used as a standard for supercritical fluid based experiments..

5.2.2 poly D, L-lactide

Both of the poly D, L-lactide polymers studied were manufactured by Boehringer Ingelheim, Germany. They are commercially known as Resomers® R104 (Mol. Wt. = 2,000) and Resomers® R202 (Mol. Wt. = 9,000) respectively.

5.2.3 Hydroxypropyl Methylcellulose (HPMC)

Hydroxypropyl Methylcellulose (Mol. Wt. = 22,000) was manufactured by the Shin-Etsu Chemical Co., Tokyo, Japan. It is an odourless and tasteless white granular powder.

5.2.4 poly Methylmethacrylate (PMMA)

poly Methylmethacrylate (Mol. Wt. = 150,000) is manufactured by, Röhm Pharma, Darmstadt, Germany. At Röhm Pharma it is known as Eudragit ®.

poly Methylmethacrylate (PMMA) RL100 is essentially a co-polymer of acrylic and methacrylic acid ester with low content of quanternary ammonium group. The ammonium group is present as a salt to make the polymer permeable. This copolymer is made up of Ethyl acrylate, Methyl methacrylate, Trimethyl-ammonioethyl Methacrylate chloride. The polymer exists in the following ratio; 1:2:0:2. Röhm Pharma refer to this ratio based PMMA as Eudragit ® RL100. The USP/NF describe it as "Ammonio Methacrylate Copolymer, Type A". It was developed in 1968. It is a polar molecule. It is a highly permeable granular solid. It is used for sustained-release formulations for oral dosage form, has neutral acid groups, therefore, it is pH independent.

5.2.5 poly D,L-lactide-co-glycolide

poly D,L-lactide-co-glycolide (Mol. Wt. = 3,000) is a co-polymer of lactide and glycolide and it exists in a 50:50 ratio. It is manufactured by, Boehringer Ingelheim, Germany as Resomers® RG502.

It is used to produce devices such as implants for the controlled release of active ingredients. The advantages of this type of polymer are:

- the degradation products – lactic or glycolic acids are metabolised in the Krebs cycle to water and carbon dioxide or excreted by the kidney.
- the polymer has been proven to be non-toxic and highly tissue compatible.

5.2.6 poly ß hydroxbuteric Acid

poly ß hydroxbuteric Acid (Mol. Wt. = 535,000) was supplied by Sigma Chemical Co., Poole, England.

5.2.7 Carbon dioxide, (CO_2).

The carbon dioxide was supplied by BOC Limited, Surrey, U.K. It complied with the British Standard, BS4105. Its specification is 99.8% pure in a liquid withdrawal cylinder pressure rated to 60 bar at 20°C.

5.2.8 Methylene Chloride

Methylene chloride also known as dichloromethane, is a clear, colourless, highly volatile liquid with ether like odour and high solvency power. With reference to the environmental concerns methylene chloride is regarded as one of the most "environmentally friendly" of volatile chemicals. A recent study on the solvent carried out by the Department of Environment has concluded that it is not a green house gas and does not contribute to the global warming. Further support comes from the US Environmental Protection Agency which does not classify methylene chloride as a photochemically reactive. It is exempt from the US Protection Agency's Air Pollution Control Regulation in the Clean Air Act of 1970, and 1977.

5.3 Pre-run Checks

Before the solubility rig can be run, the following steps were carried out:

- Pack the drying column with 5Å molecular sieve and mount the column into the rig.
- Switch on the pressure and temperature display unit.
- Turn on the cooling unit. The time taken for the drying column and pump head to get cold enough to prevent the carbon dioxide from vaporising was such that the cooler unit was left on continuously.
- Switch on the water supply to the cold trap. Insert a clean dry U-tube with a plug of glass wool, which has been weighed to ± 0.1mg, into the cold trap.
- Note the reading on the gas meter.

5.4 Start-up

This procedure was followed when starting up and operating the rig. It was important for safety considerations to follow the stages in the given order, and to wait for the conditions specified to be reached before proceeding, since operating a very high-pressure system!

5.4.1 Equilibrium Cell

Renew the O-ring seals on the end connectors of the equilibrium cell and make sure that the end connectors are clean and dry. Load the cell with the polymer under test mixed with 1.5mm balottini in order to ensure an even flow of carbon dioxide through the cell, and to bulk out polymers only available in small quantities. Install the cell in the oven and tighten the connectors.

5.4.2 Visual Check

Check the rig visually to ensure that the bypass circuit is closed and the circuit through the equilibrium cell is open (valves HV1 and HV2).

5.4.3 Pressure Test

Check the system for leaks. Close valves HV3 and TV1 and turn on the carbon dioxide and air supplies. Slowly increase the air pressure, and check for leaks around all fittings using a soap solution. The pressure should be increased to full operating pressure (600 bar) during this procedure. At the end of the check, the rig should be depressurised by

turning off the air and carbon dioxide supplies and opening valves HV3 and TV1. If a leak is detected depressurise the rig as described in section 5.5.4 to rectify the problem.

5.4.4 Heating

Switch-on the oven, and set the desired temperature. The safety thermostat should be set 10 - 15 °C above the desired temperature. Set the heat tracing tape controller to the test temperature. Leave the rig to heat up fully, for approximately one hour to reach the experimental temperature.

5.4.5 Purging System.

Turn the carbon dioxide supply on at the cylinder, and open valves LV1 or LV2 (depending on which cylinder is being used), and LV3. Open valves HV3 and TV1, and allow carbon dioxide to flow through for 5 minutes to purge air from the rig

5.4.6 Pressurise System.

Close valves HV3 and TV1. Open valve LV4 briefly (2-3 seconds) to cool the supply line to ensure liquid carbon dioxide is reaching the pump. Turn the air supply on at AV1 and slowly increase the air pressure, using the regulator AV2, until the test pressure is reached.

5.4.7 Set Flow Rate.

Open valve HV3, and use the micro-metering valve TV1 to control the flow of carbon dioxide to the desired rate (2 $LMin^{-1}$). Note the reading on the gas meter.

5.4.8 Run System

Run the system for a predetermined length of time checking the pressure and temperature regularly and adjusting if necessary. Measure and note the pressure and temperature at the gas meter inlet and outlet. The length of a run depended on the solubility of the polymer under test, as sufficient solid needs to be collected so it can be weighed accurately. For the most soluble polymers, 40 litres of carbon dioxide, at room temperature and pressure, was collected in under ½ hour, for the least soluble, 240 litres (2 hours) was required.

5.5 Shut-down

At the end of an experiment it is important to use the bypass circuit to pass pure carbon dioxide through the throttle valve (TV1). This will carry any of the test solid deposited in the line between the valves into the cold trap, and thus it can be weighed. If this is not done, the solubility measured is likely to be erroneously low. The procedure given below must be followed in the correct order, so as to obtain accurate results.

5.5.1 Operate Bypass.

Using valves HV1 and HV2 close of the flow of carbon dioxide to the equilibrium cell, and open the bypass valves which are located below HV2 and above HV1, respectively. Open valve HV3, and allow the rig to operate under flow conditions for 15 minutes. The compressed air supply to the pump, and the position of the throttle valve TV1 should not be altered at this stage.

5.5.2 Measure Volume of Carbon Dioxide.

Using valve HV3, stop the flow of carbon dioxide through the cold trap, and note the reading on the gas meter. This will give the volume of carbon dioxide used in the experiment.

5.5.3 Remove Cold Trap.

Close valve HV3, and remove the U-tube. Gloves should be worn whilst doing this to prevent traces of grease being deposited on the glass. The U-tube should be dried before re-weighing.

5.5.4 Depressurise Rig.

Insert a second U-tube, to allow the carbon dioxide to flow out of the vent rather than into the laboratory. Close HV1 to prevent carbon dioxide and polymer from flowing back into the pump. Turn the compressed air supply off at AV1 and AV2 and turn the carbon

dioxide supply off at the cylinder, and valves LV1/2 and LV3. Open valve HV3 to allow pressure to drop to atmospheric.

5.5.5 Cool Down Rig.

Switch off the oven, trace heater and the cooling system. Once the rig has cooled, and at atmospheric pressure, turn off the pressure and temperature meter, and the water supply to the cold trap.

5.6 Emergency shut-down

The following procedure should be followed if it is necessary to shut down the rig in an emergency, for example if it becomes over pressurised, or if it starts to leak. If a leak is detected, care should be taken to ensure the laboratory is well ventilated, as carbon dioxide is an asphyxiate. Steps 5.6.1 and 5.6.2 below should be carried out as quickly as possible, as these will make the rig safe.

5.6.1 Depressurise Rig.

Turn the compressed air supply off at valve AV1 and regulator AV2. Turn the carbon dioxide supply off at valve LV3 and at the cylinder. Ensure valves HV3 and TV1 are open, to allow the rig to depressurise.

5.6.2 Cool Down Rig.

Turn off the oven, trace heater, cooling system and the water supply to the cold trap. Following an emergency shut-down, the rig should be carefully examined to find why it was necessary. All problems identified should be addressed before the rig is used again. If any fittings are taken apart, the rig should be 'pressure tested' as described in section 3.7.3 as part of the next start-up procedure.

5.7 Measurements

- Pressure (bar) was monitored at the inlet and outlet to the equilibrium cell. A record of the test pressure was also made by means of a dual pressure and temperature transducer.
- Temperature (^{o}C) was monitored at the inlet and outlet to the equilibrium cell. A record of the test temperature was also made by means of a dual pressure and temperature transducer.
- Flow rate (L/Minute) was monitored so that it remains steady through the experiment, whatever the rate maybe. If the plum-bob start bopping erratically then that was a sure sign of blockage in the system and experiment had to be stopped.
- Mass (g) of U-tube was recorded before and after the experiment in order to calculate the solubility of the polymer in supercritical carbon dioxide.
- Volume of Carbon dioxide (m^3) was measured by recording the reading on the gas meter before and after the experiment. This was used to calculate the mass of carbon dioxide used in the experiment.

5.7.1 Solubility Calculations

Volume of carbon dioxide, V	=	40 dm^3 (0.04 m^3)
Temperature of carbon dioxide at gas meter, T_c	=	20°C
Pressure of carbon dioxide at gas meter, Pc	=	1 bar
Initial mass of cold trap, M_i	=	61.1784 g
Final mass of cold trap, M_f	=	61.2947 g

Calculating mass of carbon dioxide;

density, ρ, of carbon dioxide at 20°C and 1 bar	=	1. 815kg m^3
the mass of carbon dioxide used, M_{CO2}	=	ρ x V
	=	1. 815 x 0.04
	=	0.0726 kg (72.6 g).
The mass of solute collected, M_s	=	$M_f - M_i$
	=	61.2947 - 61.1784
	=	0.1163 g
Wt/Wt fraction	=	$\frac{M_s}{M_s + M_{co_2}}$
	=	$\frac{0.1163}{0.1163 + 72.6}$
	=	0.0016 g/g
% Wt/Wt fraction	=	0.16 % Wt/Wt

From the molecular mass of the solute, the mole fraction of the solute can be calculated. For the above example, it is assumed that the solute is naphthalene with a molecular mass, MM_s, of 128.

Amount of naphthalene, Ns $= \frac{M_s}{MM_s}$

$= \frac{0.1163}{128}$

$= 0.909 \times 10^{-3}$ mol.

Amount of carbon dioxide, M_{CO2} $= \frac{M_{co_2}}{MM_{co_2}}$

$= \frac{72.6}{44}$

$= 1.65$ mol.

Mole fraction of naphthalene, N $= \frac{N_s}{N_s + M_{co_2}}$

$= \frac{0.909 \otimes 10^{-3}}{0.909 \otimes 10^{-3} + 1.65}$

Mole fraction of naphthalene, N $= 0.554 \times 10^{-3}$

5.8 Validation Test

The rig was verified by measuring the solubility of naphthalene in supercritical carbon dioxide. Naphthalene was selected as the naphthalene-carbon dioxide system has been extensively studied by a number of different workers. Teskhanskaya *et al.* (1964) measured the solubility of naphthalene in supercritical carbon dioxide at conditions up to

55°C and 320 atm. This work has become a standard and was used by Kurnik *et al.* (1981) and Johnston & Eckert (1981).

The validation was carried out using crystalline naphthalene GPR (99%), supplied by BDH, Poole, U.K. Temperatures of 45 and 55°C, and pressures of 100, 150 and 200 bar were used, and each experiment was repeated at least twice to ensure reproducibility of results. The results shown in Table 5.1 and Figures 5.1 and 5.2 are in close agreement with those of Teskhanskaya *et al.* (1964). This proves that the rig operates satisfactorily and gives reproducible and accurate results.

Temperature (°C)	**Pressure (bar)**	**Solubility (mol %)**	
		Lodhi (1998)	**Teskhanskaya *et al.* (1964)**
45	100	0.009	0.006
	150	0.020	0.019
	200	0.022	0.024
55	100	0.0028	0.003
	150	0.022	0.026
	200	0.0379	0.040

***Table 5.1** Solubility of Naphthalene in supercritical carbon dioxide*

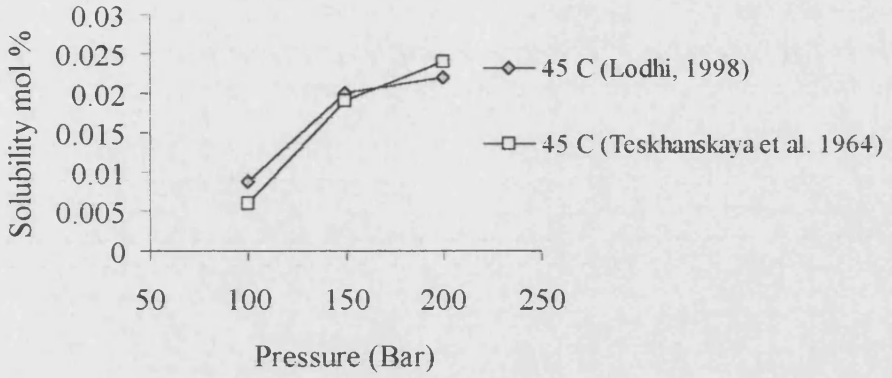


Figure 5.1 *Solubility of naphthalene in supercritical carbon dioxide at 45°C.*

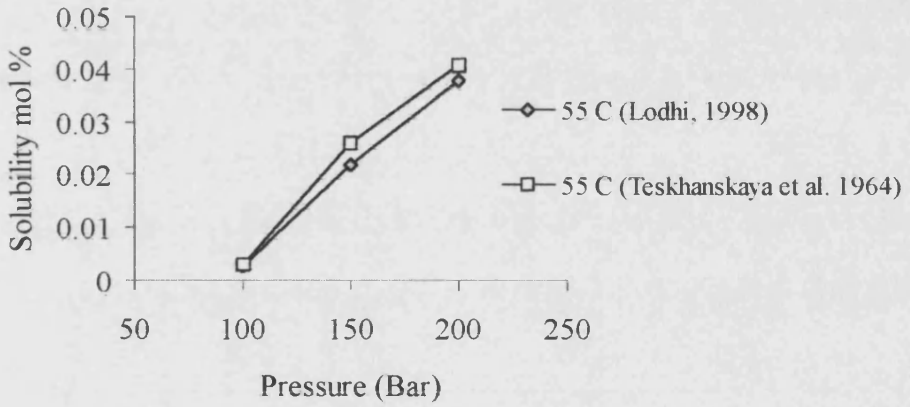


Figure 5.2 *Solubility of Naphthalene in supercritical carbon dioxide at 55°C*

5.9 Experimental for determining the solubility of polymers in $scCO_2$.

In this experiment the apparatus used is presented in Figure 4.4. Liquid Carbon dioxide was passed through a drying column to remove traces of water from the carbon dioxide. It then left the drying column to go through a non-return valve and a filter, before entering Teledyne pump. This compressed air driven reciprocating piston pump compressed the carbon dioxide to the experimental pressure before it entered the pre-heat coil. The carbon dioxide was maintained in liquid phase by ensuring that the pump heads were kept cold. Here cooled carbon dioxide was pressurised to the desired pressure by manipulating the regulating valve AV2. The pressurised carbon dioxide entered the oven that was set to the test temperature. A 3 metre length of pre-heat coil was set-up in the oven to allow the carbon dioxide to equilibrate at the test temperature and pressure prior to entering the equilibrium cell. From this point HV1 was opened gradually in conjunction with AV2 to increase the pressure in the Equilibrium Cell. Low flow rate was chosen to give carbon dioxide enough residence time to equilibrate.

Once at the experimental pressure and temperature, the carbon dioxide diffused through the packed bed of ballottini and polymer and saturated the test polymer. The carbon dioxide-rich polymer solution then exited the Equilibrium Cell via the HV2, HV3 and TV1. The TV1 was opened to a small degree as it was a control valve and adjusting this valve set the flow rate of carbon dioxide. The solubility rig was allowed to run for a predetermined length of time. The solid was collected in the pre-weighed U-tube whilst supercritical carbon dioxide escaped via the flow meter and gas meter. A plug of glass wool was included in the U-tube to prevent any particles escaping into the flow meter and blocking it.

5.10 Experimental for determining solubility in a co-solvent.

In this experimental the solubility rig was modified to incorporate a number of features (see Figure 4.6). Liquid carbon dioxide was passed through the drying column, whilst methylene chloride emerged from SP8810 pump and united with carbon dioxide at a Tee-joint before entering Teledyne pump. The flow rate of this co-solvent was set prior to starting up the rig. Both carbon dioxide and methylene chloride were pumped to the test pressure and subjected to the test temperature in the oven, before diffusing into the equilibrium cell. The solubilised polymer was collected in the U-tube cold trap together with some methylene chloride. In this case the U-tube containing a mixture of polymer and solvent was dried to evaporate any solvent before weighing. In this experiment solubility was determined in the same way as before in order to observe the enhancement, if any.

5.11 Investigating Materials Formed in the Cold trap.

Scanning Electron Microscopy (SEM) was used to study the morphology of the material left in the equilibrium cell and that collected in the cold trap. It was noticed that polymers underwent physical change in the equilibrium cell during the life of the experiment. These changes have been logged in the form SEM images and a thorough discussion is presented in chapter 7.

5.12 Scanning Electron Microscopy (SEM)

Scanning Electron Microscopy (SEM) has been used to study the external morphology of the polymers before and after subjecting to supercritical carbon dioxide and a co-solvent system.

The surfaces of poly Methylmethacrylate (PMMA), poly D,L lactide (Mol.wt. 2,000) poly D,L lactide (Mol.wt. 9,000) and poly D,L lactide-co-glycolide were studied by Scanning Electron Microscopy over some pressures and temperatures parameters. A full discussion of these results will be presented in chapter 8.

5.12.1 Introduction

Scanning Electron Microscopy (SEM) is one of the principal tools in the study of the surface or near surface structure of a specimen. In SEM based study key features need to be borne in mind; these include:

- coating technique
- the type of filament used
- acceleration voltage
- type of electron beam used to produce the image
- the spot size of the electron beam.
- and the working distance.

In this study, an electron gun of the tungsten filament is heated to temperatures in excess of 2700K to emit electrons. These electrons are accelerated at some kilo electron volts (keV) towards the microscope column, where a condenser is used to demagnify the spot size of the electron beam until it hits the specimen. The second condenser is used to focus the spot on the specimen. The spot size can be a diameter of 10-306nm. For this study of polymers only 15 keV energy was required to accelerate electrons into microscope column. The fine beam of electron of a diameter of 86nm was scanned across the specimen was by means of scan coils while the detector counts the number of low energy secondary electrons. All SEM produce *backscattered electrons*, *secondary electrons* or x-rays (see Figure 5.3). However SEM has different detectors for backscattered/secondary electron as opposed to x-rays. Secondary electrons are widely used to study the images for they can pick up more surface detail and are able to go deep into the sample unlike the other two. In this work too, secondary electrons have been the source of good image.

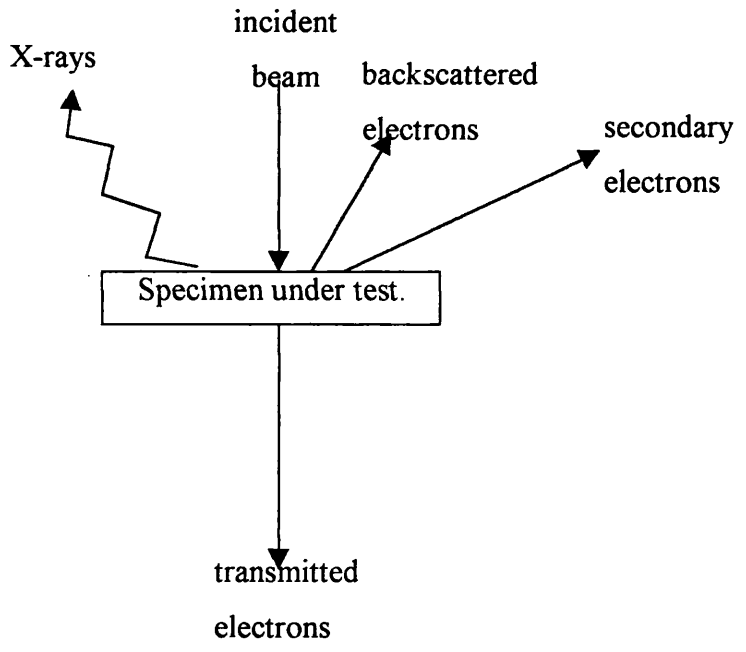


Figure 5.3 *Some of the signals which may be used in the SEM.*

The electron beam is scanned in the same way as a television receiver. The image is formed sequentially during the scan.

5.12.2 Preparation of sample

Since SEM is used to study the surface morphology, specimen does not need dissecting. The sample platform can accommodate a specimen as large as 150x150x50mm, which can be moved around in the vacuum system (10^{-5} m bar) so that largest portion can be viewed. For effective viewing of a specimen in the SEM it is usually necessary for the surface to be electrically conducting. Clearly there is no difficulty in studying metal surfaces provided that they are mounted so as to provide a conducting path to earth. However, non-conductors such as polymers and biological materials present a problem. In this case it is usual to coat the specimen with a thin (~10nm) layer of gold or carbon; this is done by a sputter coating.

The working distance is generally kept to a mid range. In my case the working distance was 17mm. Electron Microscopists' say that working distance is a matter of choice and it should result in good image. However less working distance will reduce resolution and increase the incidence of sample damage, and vice versa.

6. Results

6.1 Introduction

The major objective was to investigate an alternative from conventional liquid solvents with their associated disadvantages for solubilising coating polymers. Solubility data has been determined in pure $scCO_2$. This was determined over a range of 300 bar to 600 bar. Temperature range was chosen to be between 35°C and 60°C. 35°C was chosen to be the starting temperature to insure that the carbon dioxide had reached supercritical rich state and also because tablet coatings are generally applied at this temperature (Colorcon Ltd, 1996). Polymers were studied at temperatures ranging from 35°C to 60°C to attain a profile of solubility change across this temperature band. 60°C is the ceiling in terms of pharmaceutical application, since there are dangers that the activity of the drug may be affected at higher temperature.

Hydroxpropylmethylcellulose (HPMC), poly ß Hydroxybuteric Acid, poly Methyl-methacrylate (PMMA), poly DL lactide (Mol. Wt. =2,000), poly D,L lactide (Mol. Wt. = 9,000) and poly DL, lactide-co-glycolide, were studied in pure $scCO_2$. Following the determination of very low solubility of polymers in the pure $scCO_2$, a co-solvent was introduced to enhance solubilising power of supercritical carbon dioxide (see section 6.4). Solubility in a co-solvent system was determined at the same experimental conditions as in the pure $scCO_2$. Methylene Chloride at 2.5%(v/v) was used as the co-solvent following modifications to the experimental rig. Solubility data obtained from this co-solvent system

was significantly higher as predicted, see figures 6.8-6.14. Solubility in pure Methylene Chloride was also determined to draw comparison.

Finally, as lactide and acrylate based polymers can be obtained at different molecular weights commercially: the effect of polymer molecular weight was studied to gain an understanding of this effect in the solubility of polymers (see section 6.5).

6.2 Reproducibility and Errors

Each experiment was repeated twice to ensure that solubilities measured were as accurate as possible within the limits of the rig design. The solubility data presented in this thesis is the mean of two results. In the case of unusually low solubility data i.e. 10% lower than previous run, experiment was repeated more than twice this tended to be because the solubilised polymer was precipitating out in the micrometering valve (TV1) instead of the cold trap. In such a situation compressed carbon dioxide was pumped through at a high flow rate to flush out polymer in the micrometering valve.

Solubilised polymer was collected in the U tubes as shown in figure 6.1. Clean U-tubes were used at all times to prevent any errors in weight measurements. All U-tubes weighed approximately 60g and these were washed with the dilute nitric acid and rinsed with distilled water and finally dried in the oven to eliminate any moisture. This practice was carried out after every experiment. The U-tubes were weighed with a plug of glass wool prior to an experiment. It was so to ensure that any material that impinges on the wool plug were also weighed. The ground glass joint was sealed with a PTFE sleeve instead of

a silicon based grease; this was done to eliminate the possibility of grease getting on the neck of the U-tube which in turn would lead to inaccurate weight of U-tube.

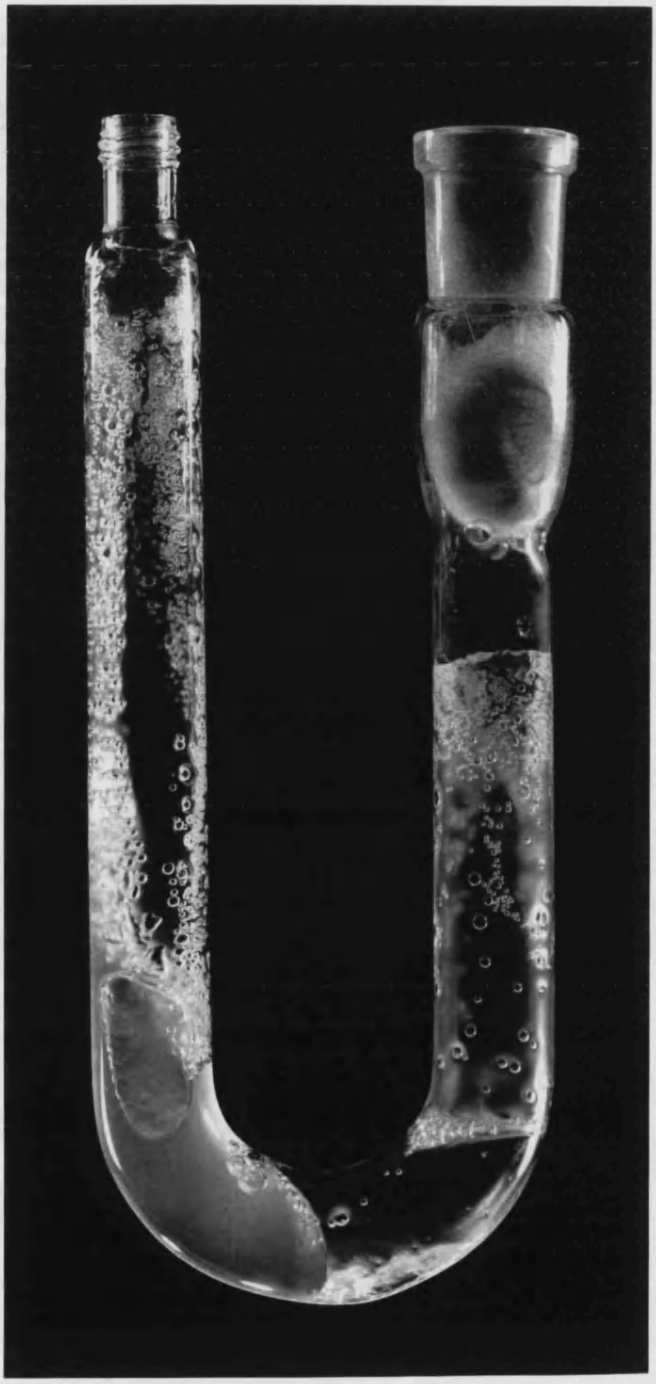


Figure 6.1 *Photograph of U-tube cold trap containing a solubilised polymer, PMMA.*

6.3 *Pure $scCO_2$ as solvent*

A number of coating polymers have been contacted with pure $scCO_2$ at pressures of up to 600 bar and temperatures of 35-60°C. Hydroxpropylmethylcellulose, (HPMC), was tested in the first instance since it is widely used in aqueous coatings for tablets. A sustained-release, water-insoluble, coating polymer, poly Methylmethacrylate (PMMA) was tested next. This particular acrylate polymer was developed for pH-independent, delayed release of active drug from the tablet core. Amongst more specialised polymers, poly ß Hydroxybuteric acid, poly D, L lactide (Mol.Wt. 2000 and 9,000), and poly D, L lactide-co-glycolide, were studied in the pure $scCO_2$. Lactide based polymers are not normally used for coating since they are used for surgical implants to provide controlled release of drug.

6.3.1. Screening Process

Solubility of the widely used coating polymers including, Hydroxypropyl Methylcellulose (HPMC), poly Methylmetharcylate (PMMA) and less widely used polymers, poly ß Hydroxybuteric acid, poly D, L lactide (Mol. Wt. = 2,000 and 9,000) and poly D, L lactide-co-glycolide was determined at the maximum operating pressure of 600 bar to observe their solubility in order to determine which polymers to study in depth. Table 6.1 below gives solubility at temperatures of 45°C and 60°C.

Preliminary solubility data revealed that poly ß Hydroxybuteric acid was completely insoluble in pure $scCO_2$ at 45°C. HPMC was the least soluble; followed by; poly DL

lactide-co-glycolide and then poly Methylmetharcylate (PMMA), poly DL-lactide (Mol. Wt.=2,000) had the highest solubility in the supercritical carbon dioxide at 45°C and closely behind was the poly D,L lactide (Mol. Wt.=9,000). At 60°C, Poly-ß-Hydroxybuteric acid was still completely insoluble in pure $scCO_2$; no polymer being collected in the pre-weighed U-tube. HPMC, PMMA and poly DL lactide-co-glycolide were sparingly soluble but again poly DL lactide was the most soluble of the studied range.

Polymer	Mol. Wt.	Solubility in $scCO_2$% (wt/wt) at 45°C	Solubility in $scCO_2$% (wt/wt) at 60°C
poly ß Hydroxybuteric acid	535,000	Insoluble within limits of detection.	Insoluble within limits of detection.
Hydroxypropylmethyl-cellulose (HPMC)	22,000	0.0015	0.0082
poly Methylmetharcylate, (PMMA) (or Eudragit® RL100)	150,000	0.046	0.0192
poly D, L-Lactide (Resomer® R104)	2,000	0.78	1.106
poly D, L-Lactide (Resomer® R202)	9,000	0.225	0.34
poly D,L lactide-co-glycolide (Resomer®RG502)	3,000	0.0214	0.038

Table6.1 *Solubility in pure $scCO_2$ at 600 bar.*

6.3.1.1 Hydroxypropylmethylcellulose, (HPMC)

HPMC was then studied at a pressure of 600 bar and at temperatures between 35°C to 60°C, to attain a solubility profile prior to further experimentation (see figure 6.2). Solubility of HPMC was found to be low in the pure supercritical carbon dioxide at 600 bar. It ranged from 0.0014%wt/wt at 35°C to 0.0082 %wt/wt at 60°C. Results collected showed that solubility increased with temperature at 600 bar in pure $scCO_2$. No further experiments were carried out in pure $scCO_2$ with this polymer other than those shown in figure 6.2, since solubility was so low and a potential of developing an economically viable coating process was considered highly unlikely.

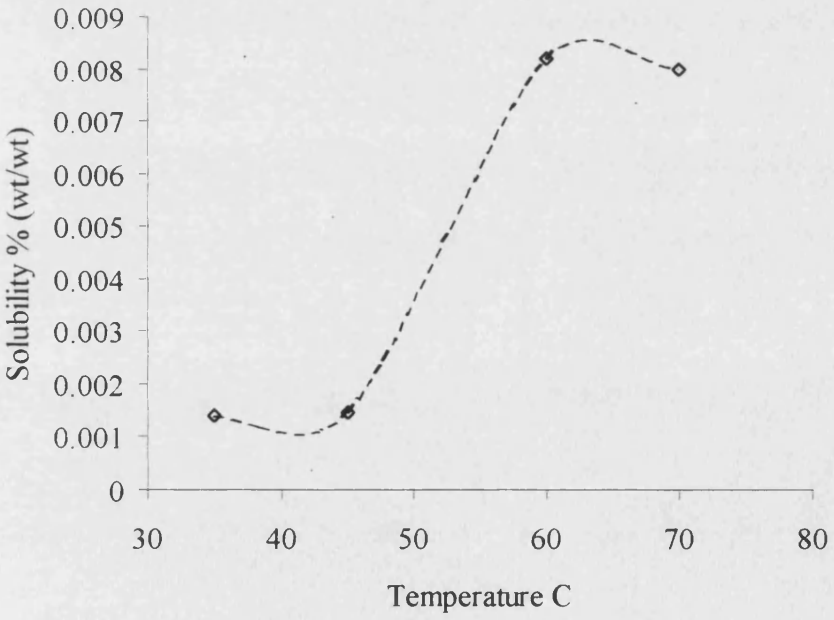


Figure 6.2. *HPMC treated with $scCO_2$ at 600 bar.*

6.3.1.2. poly Methylmethacrylate, (PMMA)

poly Methylmethacrylate (PMMA) displayed a trend of increasing solubility with increasing temperature up to a maximum and then solubility decreased across all pressure parameters studied. Overall the solubility was 1 order of magnitude higher than HPMC. At a pressure of 600 bar, maximum solubility was achieved at 45°C (0.046%wt/wt). Solubility was significantly higher (0.017 at 35°C to 0.0192 %wt/wt at 60°C) than HPMC at 600 bar for this polymer, thus this was one of the polymers chosen for further study. Figure 6.3 shows the trend of increasing solubility with increasing temperature up to a maximum.

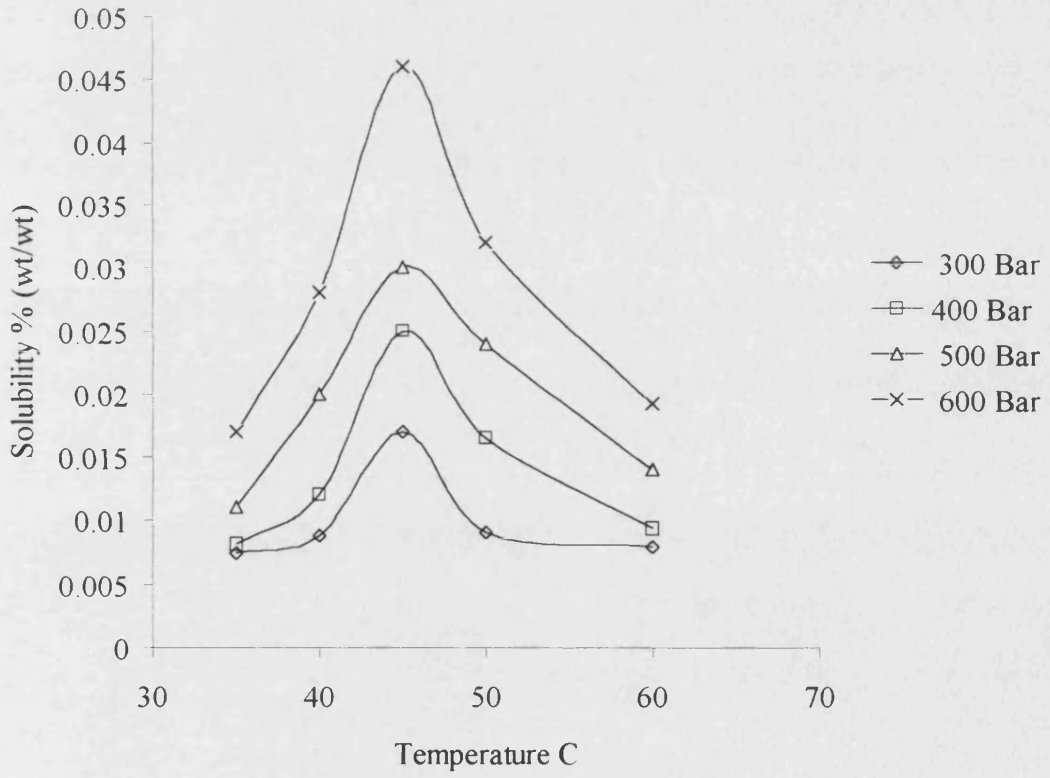


Figure 6.3 *poly Methylmethacrylate (PMMA) treated with $scCO_2$ at a range of temperatures.*

When the effect on solubility from increasing pressure (see figure 6.4) was investigated, solubility was found to increase across all the pressures studied. Solubility profile at the temperatures of 35°C, and 60°C showed low solubility. It was interesting to note that there was linear increase in solubility profile at 50°C. High solubility was recorded at 45°C across all pressure parameters in this experimental.

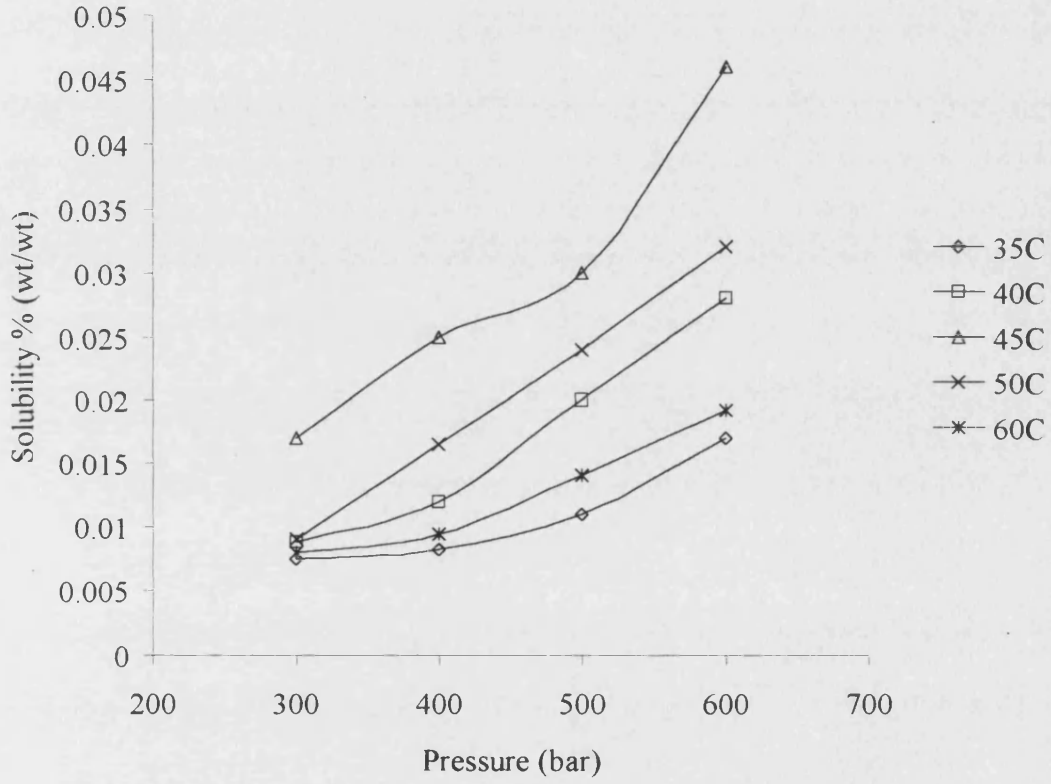


Figure 6.4 *poly Methylmethacrylate (PMMA) treated with $scCO_2$ at a range of pressures.*

6.3.1.3 poly D, L lactide (Mol. Wt. = 9,000)

poly D, L lactide at a molecular weight of 2,000 was only studied at 45°C and 60°C owing to only small quantity being available. In the case of poly DL lactide of a molecular weight of 9,000 a trend of increasing solubility was seen with increasing temperature (see figure 6.5). The solubilities determined were approximately one order of magnitude higher than poly Methylmethacrylate. At 600 bar, solubilities ranged from 0.12 %wt/wt at 35°C to 0.34 %wt/wt at 60°C in the pure $scCO_2$. Low solubilities were observed at 300bar where 0.01 % wt/wt was obtained at 35°C and this increased to 0.038 % wt/wt at 60°C. Solubility profile at 300 bar was parallel to that of 400 bar. However, notable increase was observed at 500 and 600 bar.

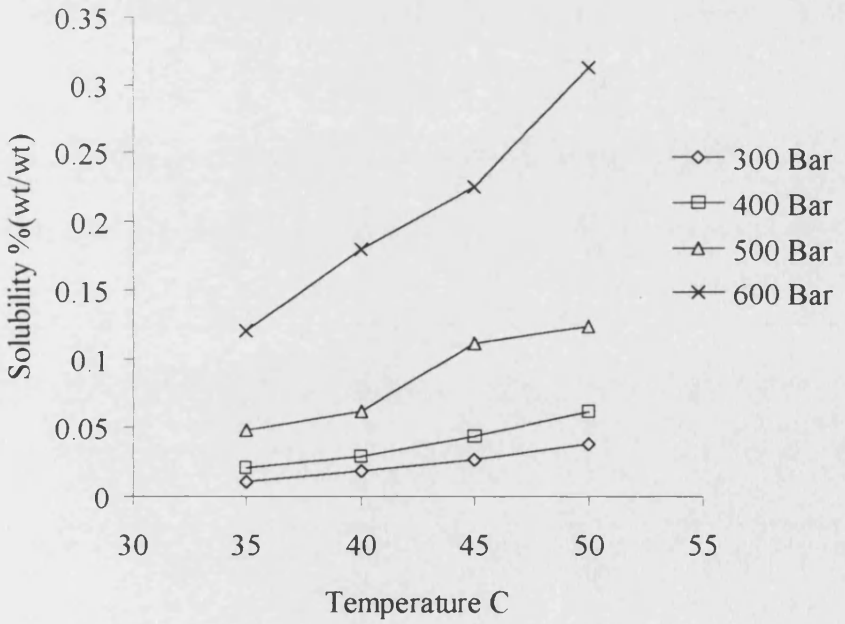


Figure 6.5 *poly D,L lactide (Mol.Wt. = 9,000) treated with the $scCO_2$ at a range of temperatures.*

The effect of pressure showed that the solubility began to increase after 400 bar (see Figure 6.6). It was anticipated that the effect of pressure will be more pronounced in relation to the effect of temperature. It is clear from the solubility data that a low molecular weight polymer, such as poly DL lactide was more soluble than the above three.

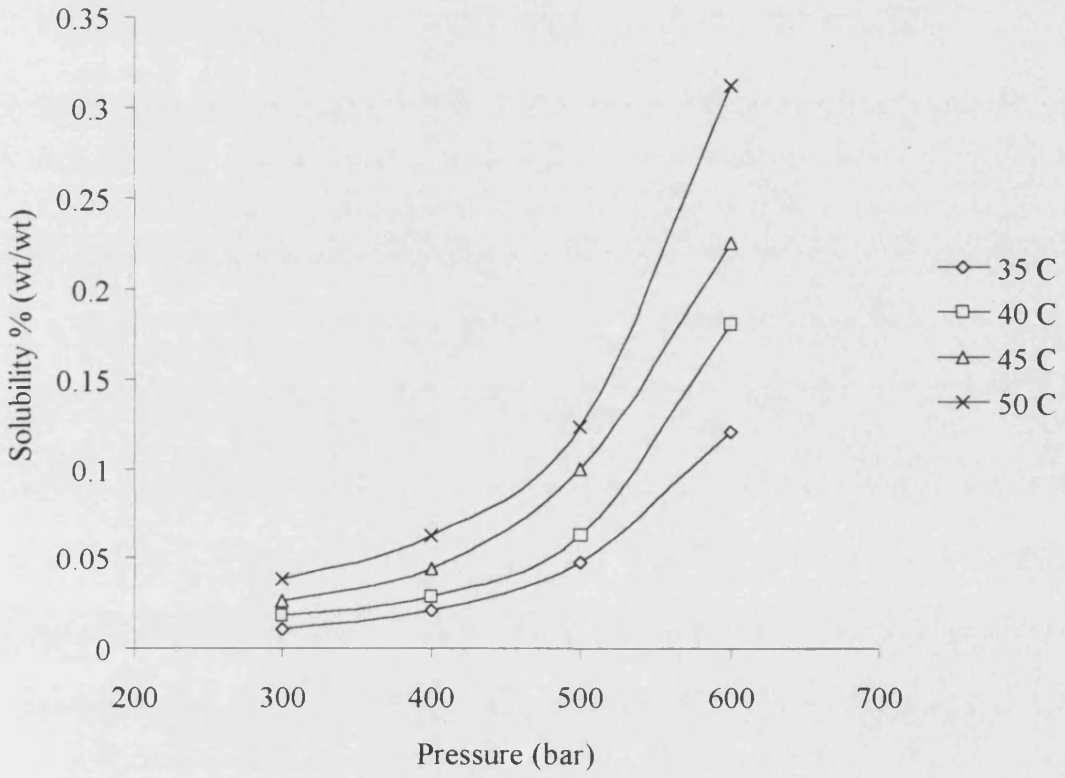


Figure 6.6 *poly D, L lactide (Mol. Wt. = 9,000) treated with $scCO_2$ at a range of pressures.*

6.3.1.4 poly D L lactide-co-glycolide

poly DL lactide-co-glycolide at 600 bar has solubility data ranging from 0.008 % wt/wt at 35°C to 0.030 % wt/wt at 60°C. The solubility profile at 600 bar stood apart from the rest of the experimental pressures. Solubility at 300, 400 and 500 bar showed a significant solubility at 45°C and above (see Figure 6.7). This data is one order of magnitude lower than poly D, L lactide (Mol.Wt. 9,000) at the same conditions. poly D, L lactide-co-glycolide was not very soluble in the pure supercritical carbon dioxide.

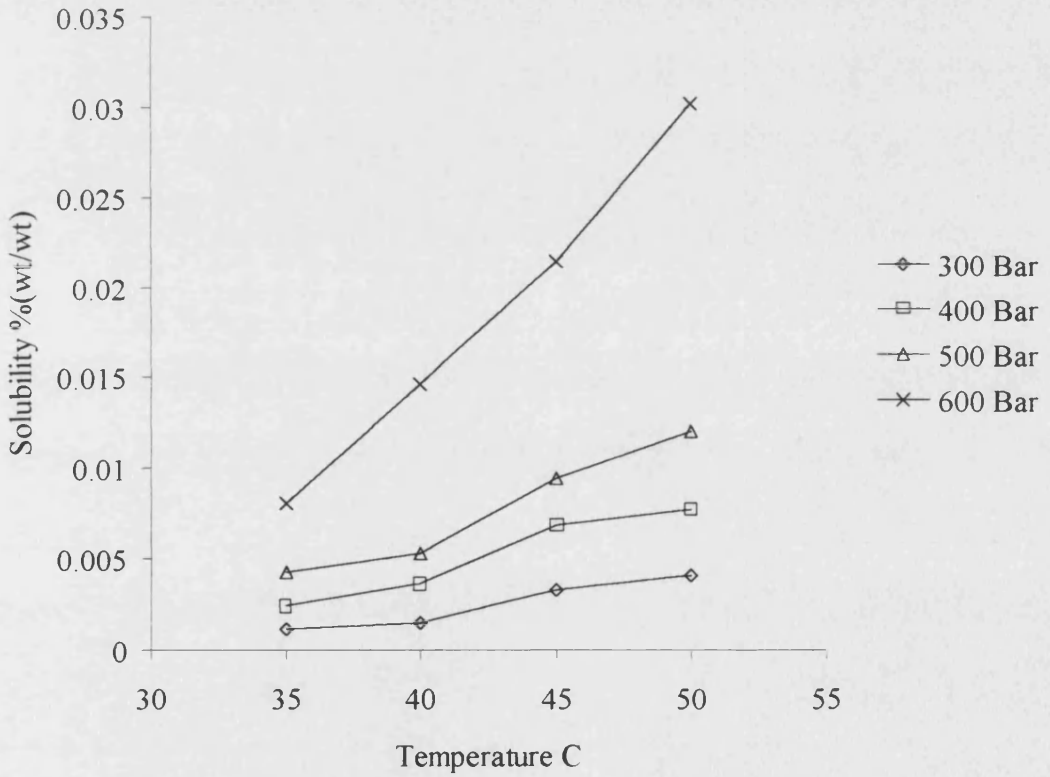


Figure 6.7 *poly D, L lactide-co-glycolide treated with $scCO_2$ at a range of temperatures.*

The effect of pressure (see Figures 6.8) showed solubility increased with increasing pressure. At 600 bar solubility of 0.0302 % w/w was noted at 50°C. An investigation for pressures between 500 and 600 bar would have been advantageous to see how profiles could have developed.

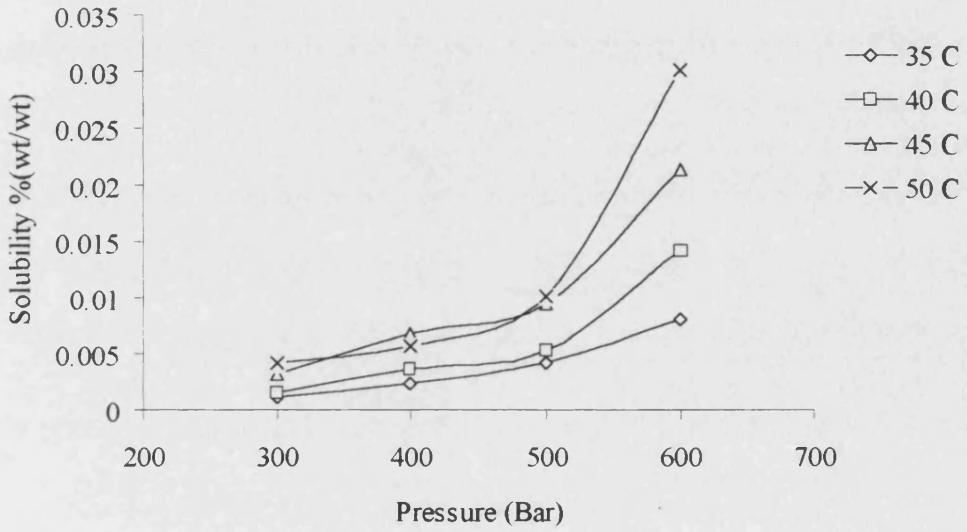


Figure 6.8 *poly DL lactide-co-glycolide treated with $scCO_2$ at a range of pressures.*

6.4 *Methylene chloride as a solvent*

Solubility of the polymers in pure methylene chloride was determined using a Bohlin Rheometer. Shear stress and shear rate was measured for a range of concentrations and viscosities were calculated. The solubility of the polymers was determined from a plot of viscosity versus concentration of the polymer in methylene chloride (see table 6.2). A transition between gel and solution is shown by a change in gradient of the plot and this point corresponds to the solubility of the polymer in the solvent.

Polymer	Mol. Wt.	Solubility in pure Methylene chloride %(wt/wt).
HPMC	22,000	-
PMMA	150,000	0.830
poly DL lactide	9,000	0.641
poly DL lactide-co-glycolide	3,000	2.047

Table 6.2. *Solubility in pure methylene chloride at 1 bar and 10°C*

6.5 *$scCO_2$ - Methylene chloride system*

A 2.5% (v/v) liquid Methylene chloride stream was mixed with the supercritical carbon dioxide prior to entering the Equilibrium Cell, which was packed with the test polymer. The *$scCO_2$* - Methylene chloride system was used to enhance the solubility of polymers as it is well known that addition of a small percentage of a co-solvent can substantially increase the solubility of a polymer (Kiamos *et al*, 1994) but polymers of pharmaceutical

interest have not been studied before. 2.5 % (v/v) was used because pharmaceutical coating formulators want to reduce organic solvent usage to a maximum of 5%(v/v) (Merrifield, 1998).

Solubilities of polymers of hydroxypropylmethylcellulose (HPMC), poly Methyl metharcylate (PMMA), poly DL lactide and poly DL lactide-co-glycolide were determined in $scCO_2$ - Methylene chloride system, between pressures of 300-600 bar. Solubility increased considerably in the presence of this co-solvent, as shown in the results below.

6.5.1. Hydroxypropylmethylcellulose, (HPMC)

Solubility was enhanced by 2 orders of magnitude when 2.5% (v/v) the liquid methylene chloride was used in conjunction with the $scCO_2$. Solubility increased with increasing temperature (see Figure 6.9) at 600 bar. Maximum solubility of 1.226 %wt/wt was achieved at 70°C but this was not useful from the pharmaceutical perspective as coating is carried out 35°C. Furthermore, the fact remains that the solubilities obtained were not significant enough to consider more experimentation on this polymer, as these would not enable a full size economic process. Supercritical fluid based process will be in competition with existing aqueous coating technology.

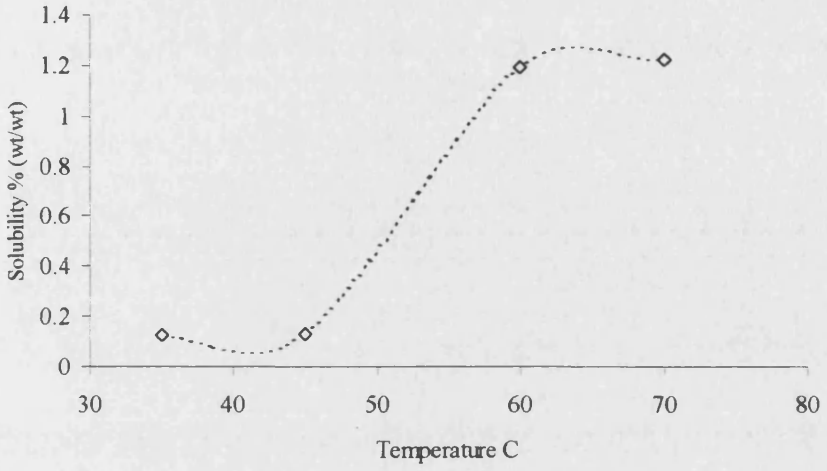


Figure 6.9 *HPMC treated with $scCO_2$ - Methylene chloride system at 600 bar.*

6.5.2. poly Methylmethacrylate, (PMMA).

Solubility increased with increasing temperature (see Figure 6.10) in the $scCO_2$ - Methylene chloride system. A pronounced effect of temperature was realised at 600 bar where a solubility of 8.211 %wt/wt was found at 60°C. From the solubility profiles it can be seen that there was a steady increase across the experimental temperatures. Determination of solubility at temperatures greater than 60°C would have been interesting but time constraints prevented it. Solubility increased by 2 orders of magnitude in the $scCO_2$ - Methylene chloride system in comparison to solubility in the pure $scCO_2$.

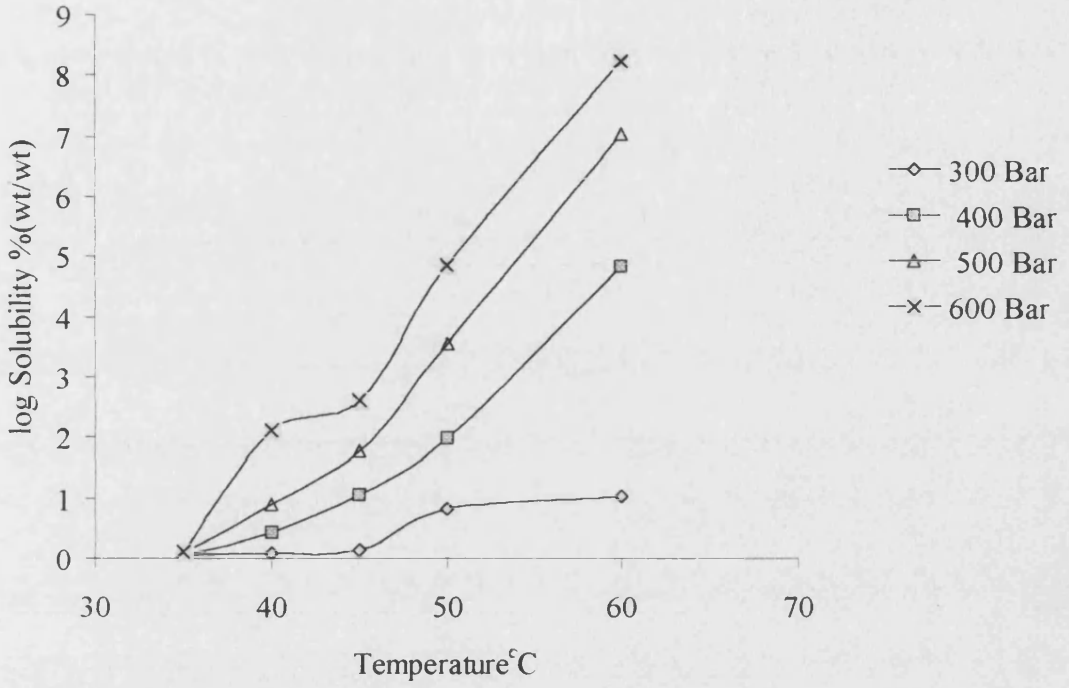


Figure 6.10 *poly Methylmethacrylate treated with $scCO_2$ - 2.5%(v/v) Methylene chloride system at a range of temperatures.*

Solubility also increased with increasing pressure in $scCO_2$ - Methylene chloride system (see figure 6.11). The effect of increasing pressure resulted in significantly high solubility throughout all temperatures in relation to those in the pure $scCO_2$. At 60°C and 600 bar solubility increased to 8.211 %w/w. The addition of a co-solvent system has enhanced the solubility of PMMA by 2 orders of magnitude.

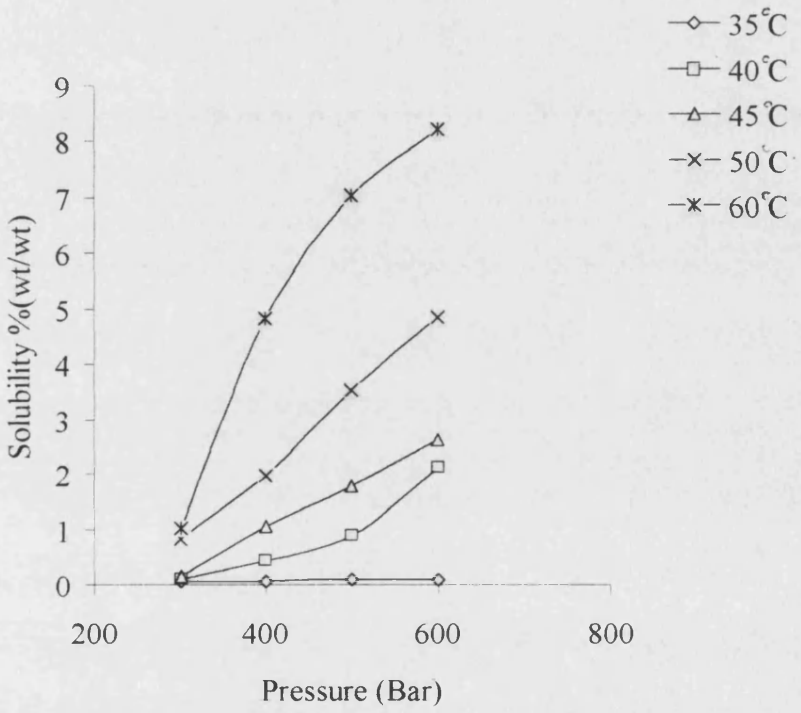


Figure 6.11 *poly Methylmethacrylate treated with $scCO_2$ - 2.5%(v/v) Methylene chloride system at a range of pressures.*

6.5.3. poly D, L lactide (Mol. Wt. = 9,000)

Solubility increased with increasing temperature (see Figure 6.12) in the $scCO_2$ - Methylene chloride system. At 600 bar the solubility was found to increase from 2.11 %wt/wt at 35°C to 6.23 %wt/wt at 60°C. This polymer was 20 fold more soluble in the $scCO_2$ - Methylene chloride system at temperature of 35°C, than that determined in the pure $scCO_2$ at the same conditions.

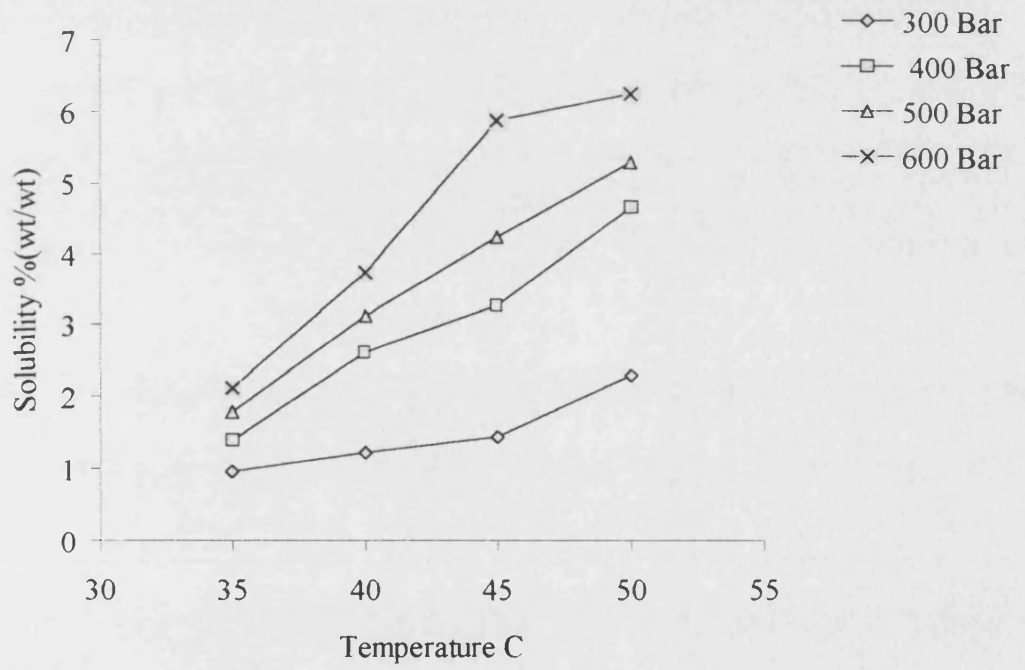


Figure 6.12 *poly DL lactide treated with $scCO_2$ - 2.5%(v/v) Methylene chloride system at a range of temperatures.*

Solubility increased with increasing pressure over a range of temperatures (see Figure 6.13) in the $scCO_2$ - Methylene chloride system. This was a non-polar, low molecular weight polymer, unlike the PMMA and therefore, solubilities were not expected to increase by 2 to 3 orders of magnitude on treating with the $scCO_2$ - Methylene chloride system. As a result solubility increased by approximately 20 fold at same conditions in relation to those determined in the $scCO_2$.

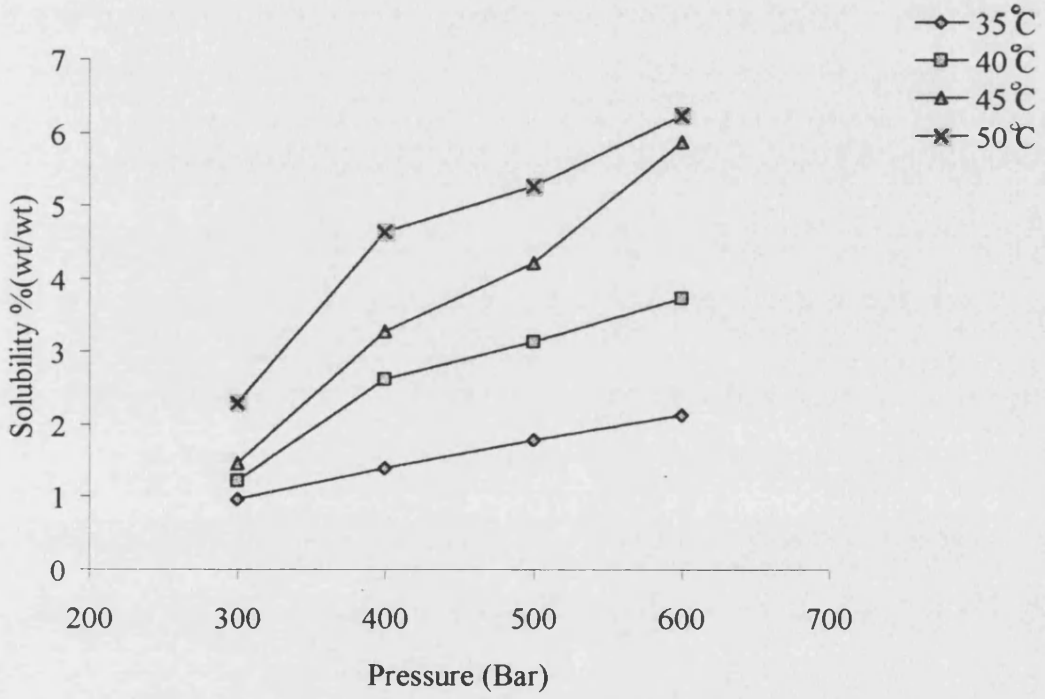


Figure 6.13 *poly DL lactide treated with $scCO_2$ - 2.5%(v/v) Methylene chloride system at a range of pressures.*

6.5.4. Poly DL lactide-co-glycolide

The effect of increasing temperature had the result of increasing solubility (see Figure 6.14) up to a maximum for the poly DL lactide-co-glycolide. At 600 bar the solubility increased from 0.727 % wt/wt at 35°C to 9.69 % wt/wt at 50°C, reaching a maximum solubility at 45°C with 10.99 % wt/wt in the $scCO_2$ - Methylene chloride system. In the pure supercritical carbon dioxide system it was not very soluble and the addition of 2.5 % (v/v) of Methylene chloride has led to an increase in solubility. A 500 fold at 45°C to 100 fold at 60°C was found in relation to those determined in the $scCO_2$ at a pressure of 600bar.

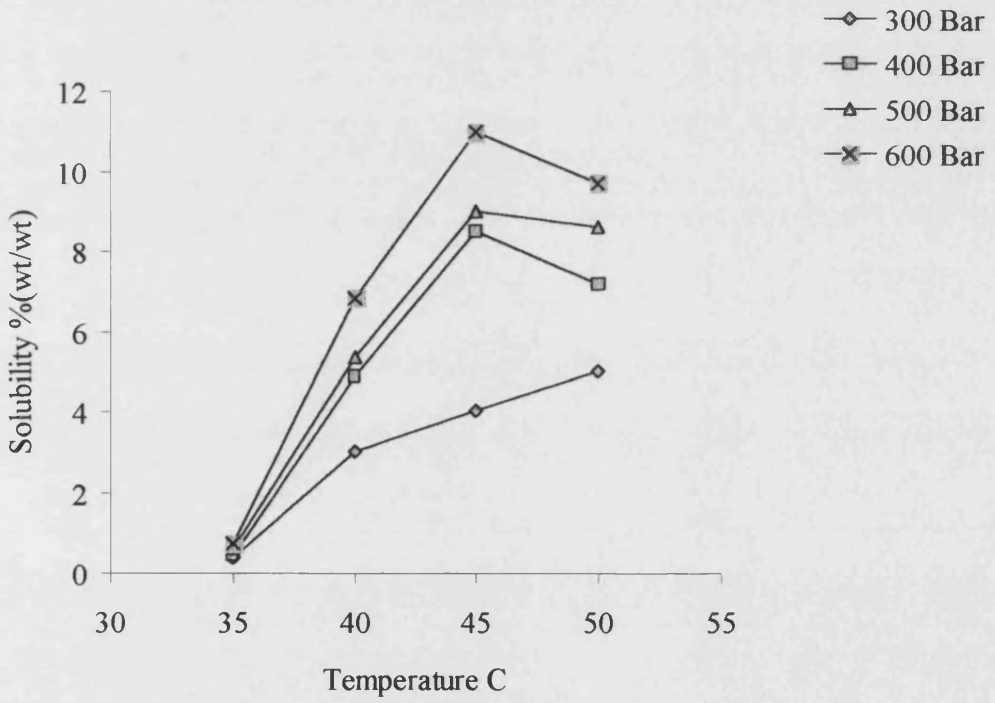


Figure 6.14 *poly DL lactide-co-glycolide treated with $scCO_2$ - 2.5%(v/v) Methylene chloride system at a range of temperatures*

Increase in solubility with increasing pressure was observed for poly D, L lactide-co-glycolide (see Figure 6.15) in the $scCO_2$ - Methylene chloride system. The solubility was highest at 45°C across majority of the pressures.

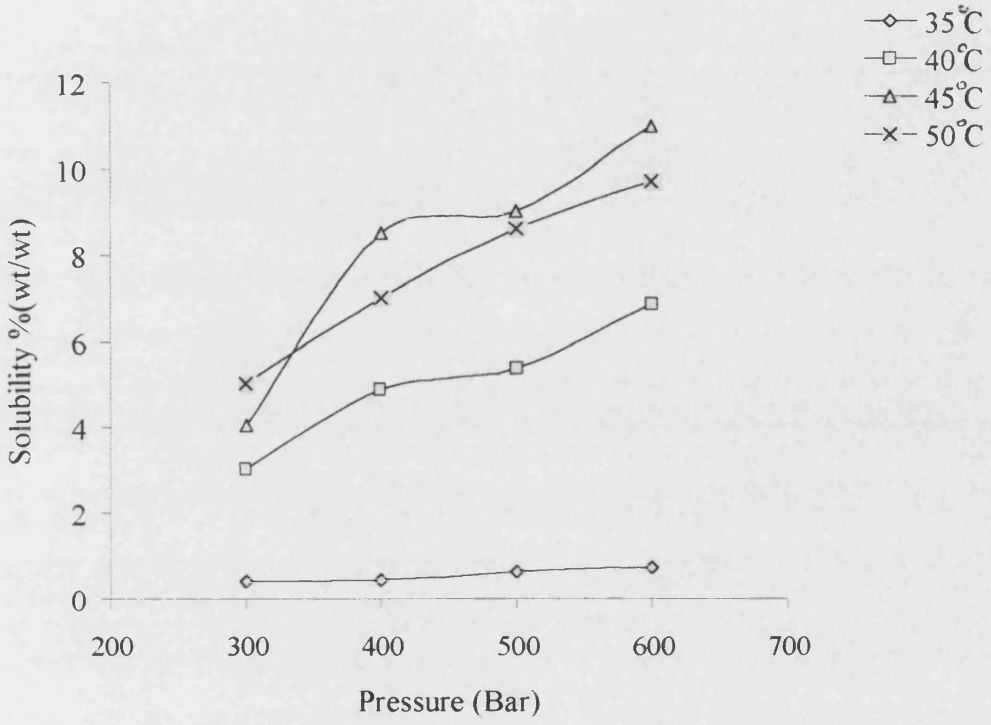


Figure 6.15 *Solubility of poly D, L lactide-co-glycolide when treated with $scCO_2$ - 2.5%(v/v) Methylene chloride system at a range of pressures*

6.6 Molecular Weight

It has been observed that increasing the molecular weight has the effect of reducing solubility with pure $scCO_2$. This solubility is enhanced by some orders of magnitude for high molecular weight polymers when 2.5% (v/v) methylene chloride was used with pure $scCO_2$. It has been observed that solubility decreased by approximately one order of magnitude as the molecular weight increased by the same.

Table 6.3. *Summary of Solubility Results*

Polymer	Mol. Wt.	Temp(°C)	Pressure (bar)	Solubility % wt/wt	
				$scCO_2$	$scCO_2$ – Methylene Chloride
poly ß Hydroxbuteric acid	535,000	45	300	–	–
		60		–	–
		45	600	–	–
		60		–	–
HPMC	22,000	35	600	0.0014	0.124
		45		0.0015	0.132
		60		0.0082	1.192
		70		0.0080	1.226
PMMA	150,000	35	600	0.0172	0.092
			500	0.0112	0.076
			400	0.0082	0.064
			300	0.0074	0.051
		40	600	0.0280	2.112
			500	0.0211	0.880
			400	0.0120	0.423
			300	0.0088	0.0912
		45	600	0.0460	2.621
			500	0.0300	1.780
			400	0.0250	1.044
			300	0.0172	0.140

		50	600	0.0321	4.850
			500	0.0241	3.543
			400	0.0165	1.970
			300	0.0090	0.820
		60	600	0.0192	8.211
			500	0.0140	7.022
			400	0.0095	4.820
			300	0.0080	1.022
poly D, L lactide	2,000	45	600	0.7801	_
		60		1.1060	_
poly D, L lactide	9,000	35	600	0.1202	2.116
			500	0.0480	1.780
			400	0.2120	1.400
			300	0.0100	0.960
		40	600	0.1811	3.720
			500	0.0620	3.120
			400	0.0292	2.620
			300	0.0180	1.220
		45	600	0.2250	5.860
			500	0.1110	4.220
			400	0.0440	3.270
			300	0.0260	1.450
		50	600	0.3121	6.230
			500	0.1230	5.270
			400	0.0621	4.651
			300	0.0381	2.312
		60	600	0.3412	_

poly D,L lactide-co-glycolide	3,000	35	600	0.0080	0.727
			500	0.0042	0.612
			400	0.0024	0.421
			300	0.01102	0.040
		40	600	0.0146	6.841
			500	0.0053	5.360
			400	0.0036	4.882
			300	0.0015	3.011
		45	600	0.0214	10.992
			500	0.0094	9.012
			400	0.0068	8.503
			300	0.0032	4.040
		50	600	0.0302	9.690
			500	0.0012	8.610
			400	0.0077	7.040
			300	0.0041	5.020
		60	600	0.0380	-

7. SEM Results

7.1 Aim

Scanning Electron Microscopy (SEM) has been used to study the external morphology of the polymers before and after subjecting to supercritical carbon dioxide and a co-solvent system.

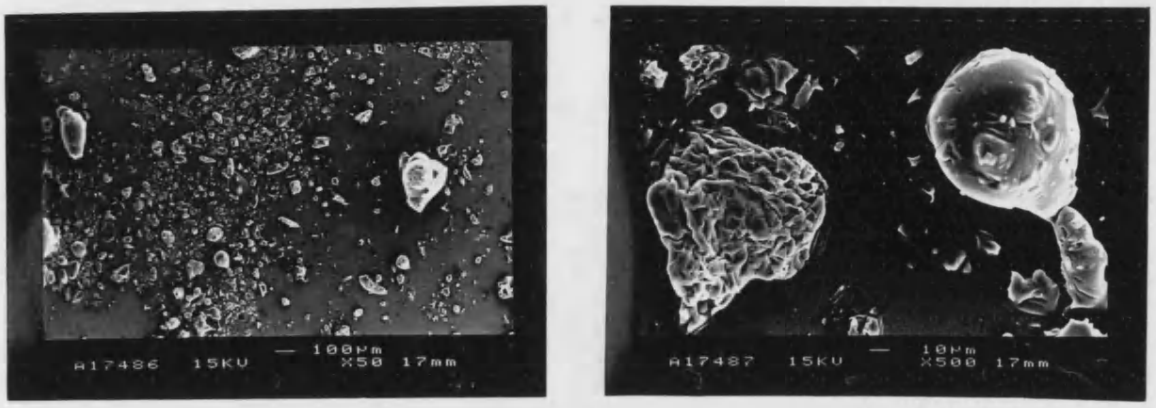
The surfaces of poly Methylmethacrylate (PMMA), poly DL lactide (Mol.wt. 2,000) poly DL lactide (Mol.wt. 9,000) and poly DL lactide-co-glycolide were studied by Scanning Electron Microscopy. After being subjected to a range of pressures and temperatures in the solubility rig the polymer was collected in the cold trap for examination by SEM. A full discussion of these observations will be presented in chapter 8.

7.2 $scCO_2$ samples.

In the first instance untreated polymers were scanned at low magnification (x50) to capture overall detail and later at high magnification to observe the surface details. The polymers were then contacted with pure supercritical carbon dioxide over a range of temperatures and pressures. There was a significant change in the surfaces of the polymers in pure supercritical carbon dioxide as the temperature and pressure was increased.

7.2.1 poly D, L lactide (Mw= 2,000)

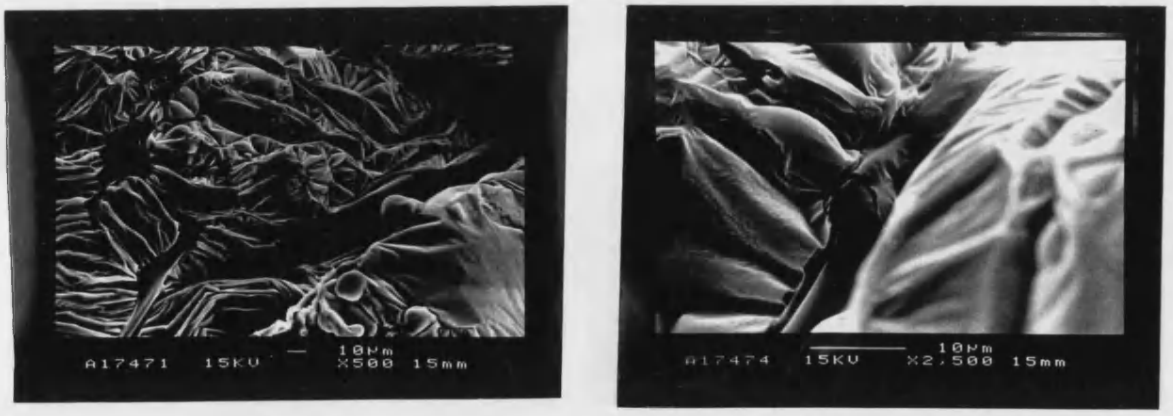
Untreated poly DL lactide is an amorphous white solid powder of a electrostatic nature. At a magnification of x500 (see figures 7.1b) particles were found to be of an irregular shape with deep folds.



(a) (b)

Figure 7.1 *Untreated poly D, L lactide at (a) x50, (b) x500 magnification*

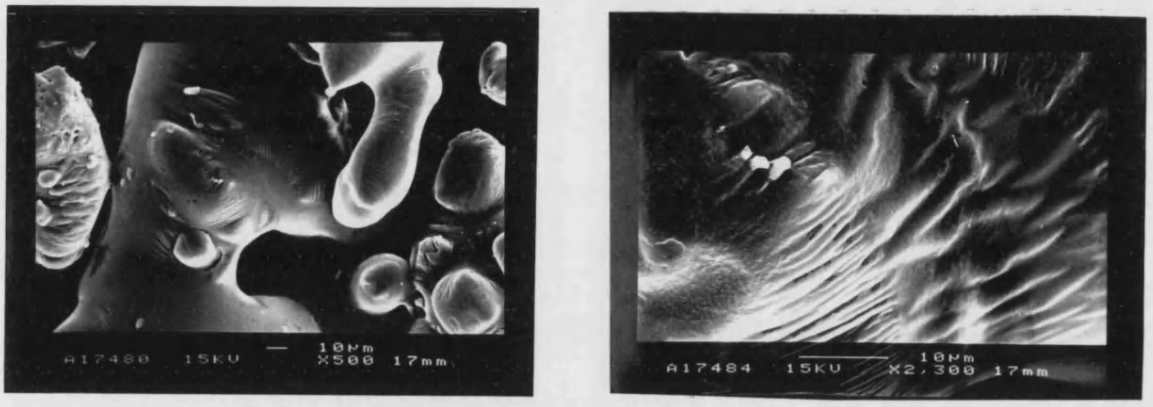
When poly DL lactide was treated with pure $scCO_2$ at 45°C and 600 bar (see figure 7.2a and b), a white gel was collected in the cold trap. On examination by SEM, irregular folds bearing smooth surface were observed. At x2500 these folds appeared to be inflated air pockets.



(a) (b)

Figure 7.2 *poly D, L lactide treated at 45°C and 600 bar in $scCO_2$ (a) x500 (b) x2500 magnification.*

At 60°C an inflated thin plastic bubble-like surface was seen and on a closer examination (x2300) this did not have deep folds, unlike the image in figure 7.2b. Figures 7.3a and b show the effect on morphology on subjecting polymer to 60°C and 600 bar in $scCO_2$.



(a) (b)

***Figure** 7.3 poly D, L lactide treated at 60°C and 600 bar in $scCO_2$ (a) x500, (b) x2300 magnification.*

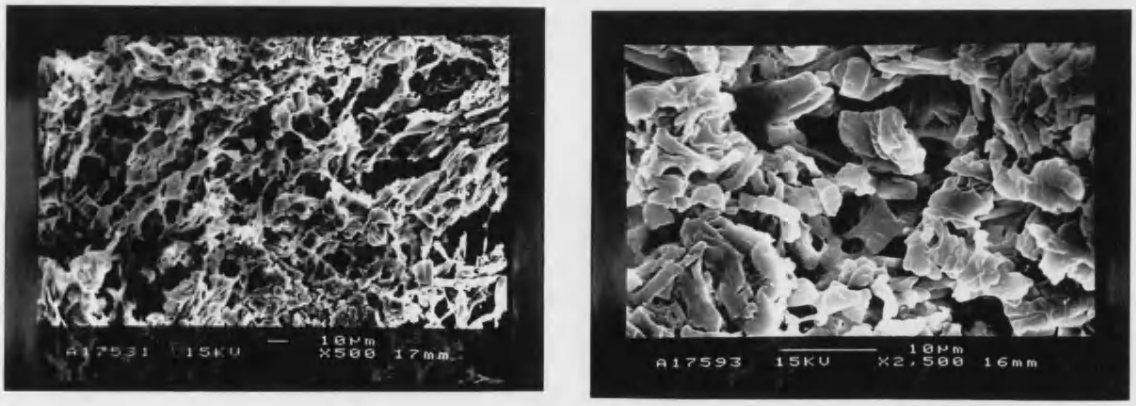
7.2.2 poly D, L lactide (Mol. Wt.= 9,000)

Untreated poly D, L lactide is an amorphous white solid powder of a electrostatic nature of a molecular weight of 9000. At a magnification of x500 several particulate can be seen and these are of an irregular shape. At x2500 a spore like structure is seen this is understandable as the polymer powder has not yet been contacted with any solvent (see figures 7.4a and b).

(a) (b)

Figure 7.4 *Untreated poly D, L lactide Mol.wt 9,000 at (a) x500 (b) x2500 magnification.*

At 35°C and 600 bar the polymer was observed to have interconnecting strands. This suggests that even at low temperatures supercritical carbon dioxide was plasticising the polymer (see figure 7.5a). At higher magnification these joined strands were very distinct (see figure 7.5b).



(a) (b)

Figure 7.5 *poly D, L lactide treated at 35°C and 600 bar in $scCO_2$ (a) x500 (b) x2500 magnification.*

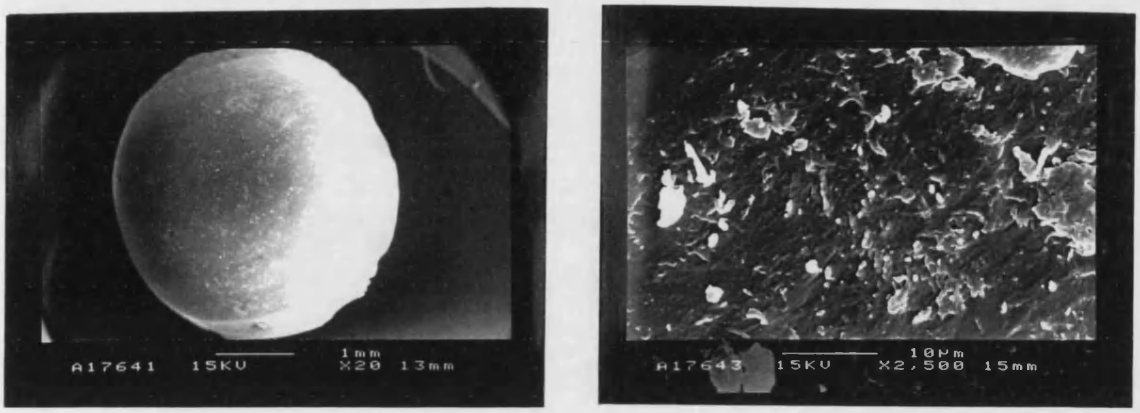
Increasing the temperature by 10°C to 45°C has the effect of further plasticising the polymer. A continuous but folded surface is observed. This surface is not hollow in places, as figures 7.6a and b show.

(a) (b)

Figure 7.6 *poly D, L lactide treated at 45°C and 600 bar in $scCO_2$ (a) x500 (b) x2500 magnification.*

7.2.3 poly Methylmethacrylate (Mw= 150,000)

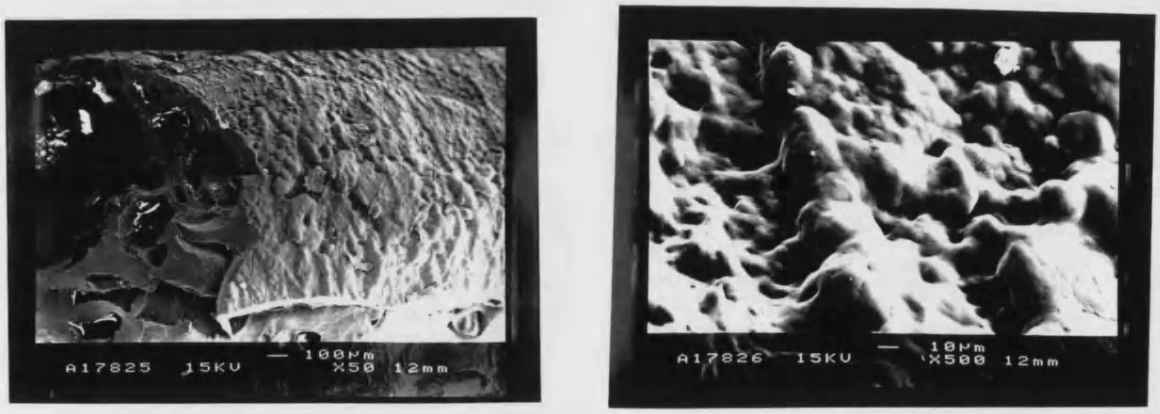
The untreated polymer is a colourless solid spherical granule (see figure 7.7a). At higher magnification it is apparent (see figure 7.7b) that surface is not smooth in fact it is rough and powder is anchored in the crevices



(a) (b)

Figure 7.7 *Untreated poly Methylmethacrylate at (a) x20, (b) x2500 magnification.*

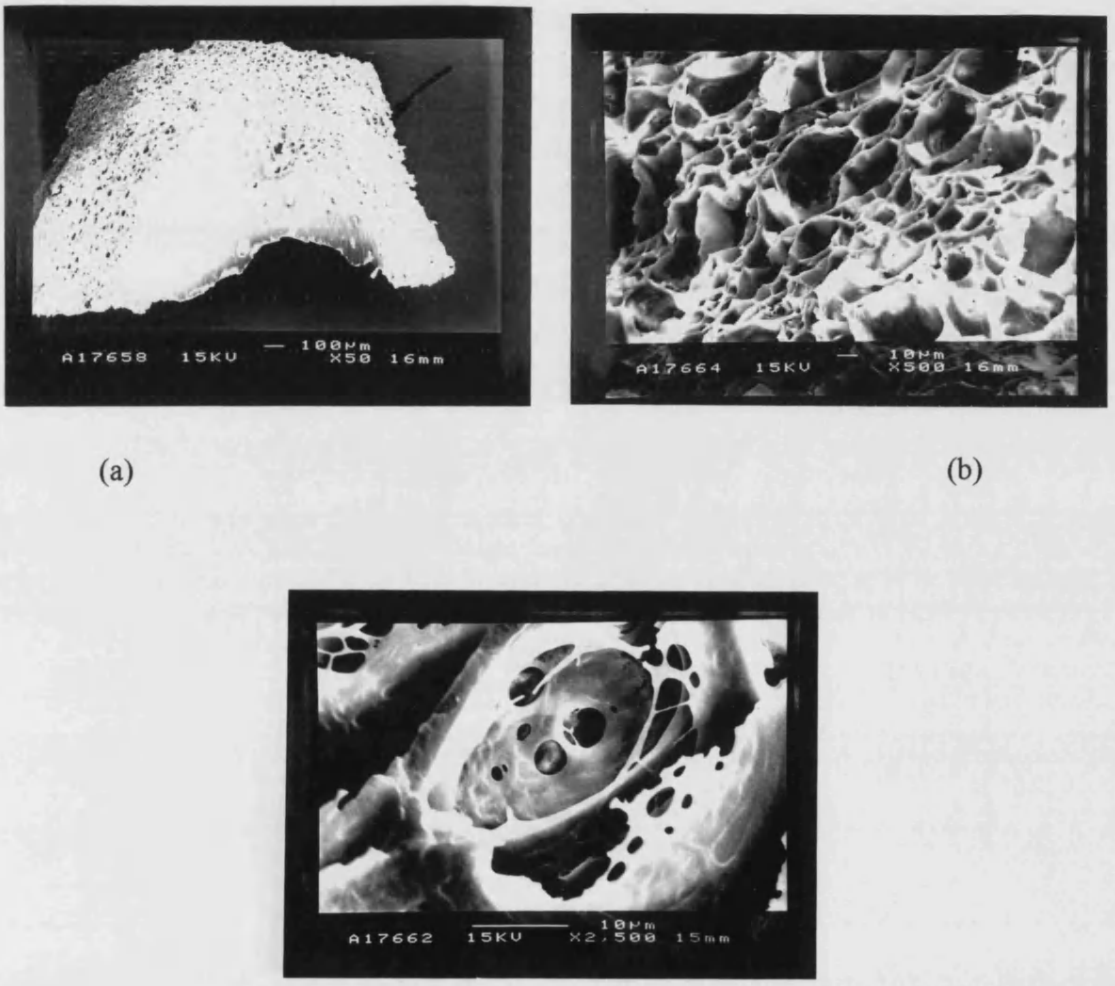
At 300 bar and 40°C the granules have disappeared. The polymer collected in the cold trap has smooth folds across the surface. Folds are prominent at x500 (see figures 7.8a and b).



(a) (b)

Figure 7.8 *poly Methylmethacrylate treated at 40°C and 300 bar in $scCO_2$ (a) x50, (b) x500 magnification.*

At 600 bar and 40°C porous white solid polymer was collected. At a magnification of x50 it looks like a porous rock (figure 7.9a). On further magnification (figure 7.9b) those pores have wafer thin side-walls. At x2500 (figure 7.9c) individual pores were found to have holes in them and appeared brittle in nature.



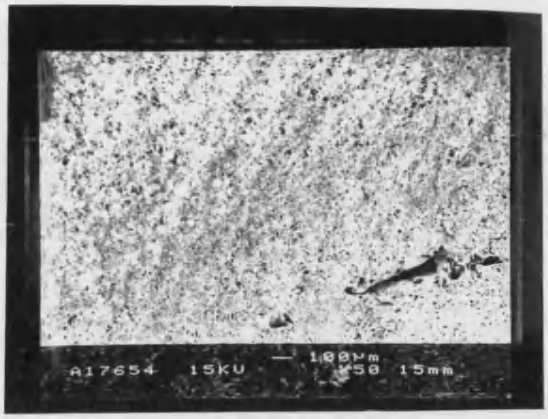
(a) (b)

(c)

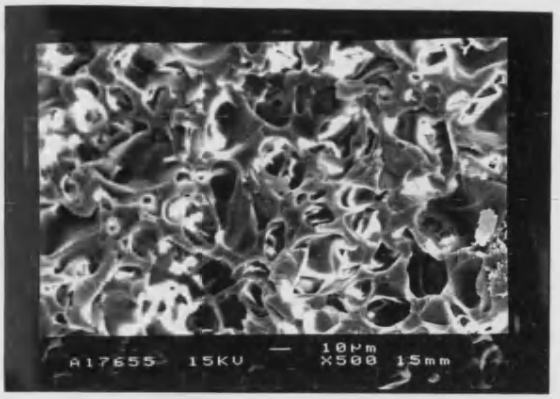
Figure 7.9 *poly Methylmethacrylate treated at 40°C and 600 bar in $scCO_2$ (a) x50 (b) x500 (c) x2500 magnification.*

At 600 bar and 60°C, the white solid was supporting porous (figure 7.10a) structure. However at a higher magnification a hollow surface was seen but the walls were thicker

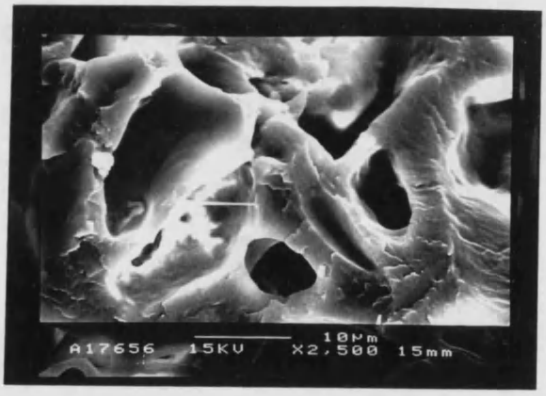
(figure 7.10b); unlike the polymer in figure 7.9b. At a magnification of x5000 the pores seemed to be supported by thick walls (figure 7.10c).



(a)



(b)



(c)

Figure 7.10 *poly Methylmethacrylate treated at 60°C and 600 bar in $scCO_2$ (a) x50, (b) x500 (c) x2500 magnification*

7.3 *$scCO_2$ – Methylene Chloride system.*

2.5 % v/v Methylene chloride was added to the supercritical carbon dioxide and this mixture was contacted with all the polymers studied, however only some of those were studied under SEM. These included poly D, L lactide (mw=9,000), poly D, L lactide-co-glycolide and poly Methylmethacrylate. Polymeric films were also produced from PMMA.

7.3.1 Poly D, L lactide (Mol. Wt. = 9,000)

In a co-solvent system polymer at 35°C and 600 bar was found to be more gel like and colourless. The surface has amazing entwined plaits.

(a) (b)

Figure 7.11 *poly D, L lactide treated at 35°C and 600 bar in $scCO_2$ – Methylene Chloride system (a) x500, (b) x2500 magnification.*

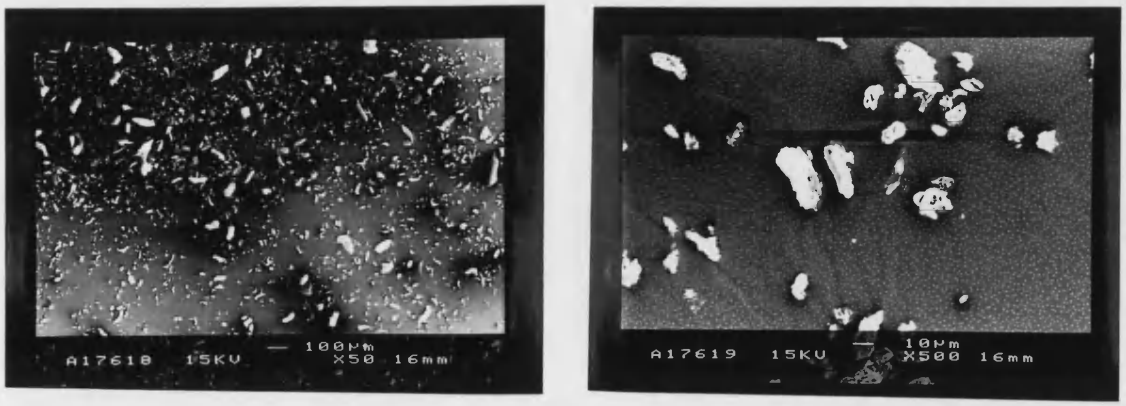
At 45°C and 600 bar, the polymer formed uniform folds across the entire surface. These folds were shallow (see figure 7.12a). At higher magnification these folds do not look so uniform but they certainly have a inflated plastic look (figure 7.12b).

(a) (b)

Figure 7.12 *poly D, L lactide treated at 45°C and 600 bar in $scCO_2$ – Methylene Chloride system (a) x500 (b) x2500 magnification.*

7.3.2 poly D,L lactide-co-glycolide (mw = 3,000)

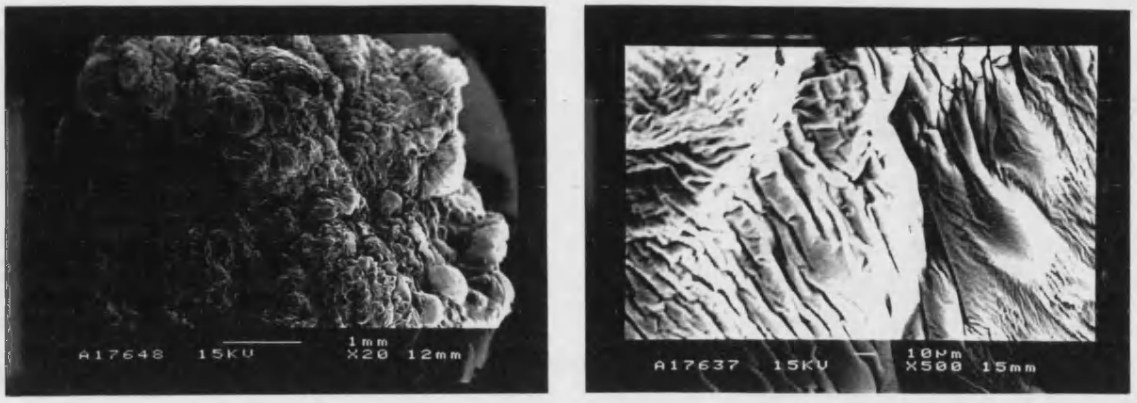
poly D,L lactide-co-glycolide (mw = 3,000) was not tested in pure $scCO_2$ due to the accidental loss of those samples. In a co-solvent system poly D, L lactide-co-glycolide came up as gelatinous and colourless polymer. In its unreacted state it is white solid powder (see figure 7.13a and b) and extremely electrostatic.



(a) (b)

Figure 7.13 *Untreated poly D, L lactide at (a) x50 (b) x500 magnification*

After treatment at 35°C and 600 bar, the polymer surface had gone from isolated particles to a gel like viscous medium. The surface had folds (see figure 7.14a and b).



(a) (b)

Figure 7.14 *poly D, L lactide-co-glycolide treated at 35°C and 600 bar in $scCO_2$ – Methylene Chloride system (a) x20, (b) x500 magnification.*

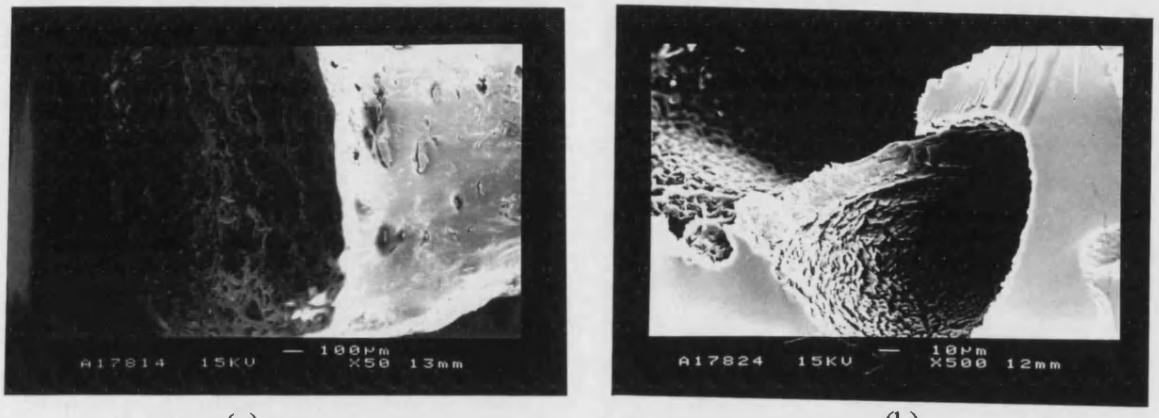
The nature of the polymer changed considerably less than expected. The polymer had plasticised as is evident from figure 7.15a. At higher magnification the surface appears to have some folds figure 7.15b.

(a) (b)

Figure 7.15 *poly D, L lactide-co-glycolide treated at 45°C and 600 bar in $scCO_2$ – Methylene Chloride system (a) x500, (b) x2500 magnification*

7.3.3 poly Methylmethacrylate (Mol.Wt. = 150,000)

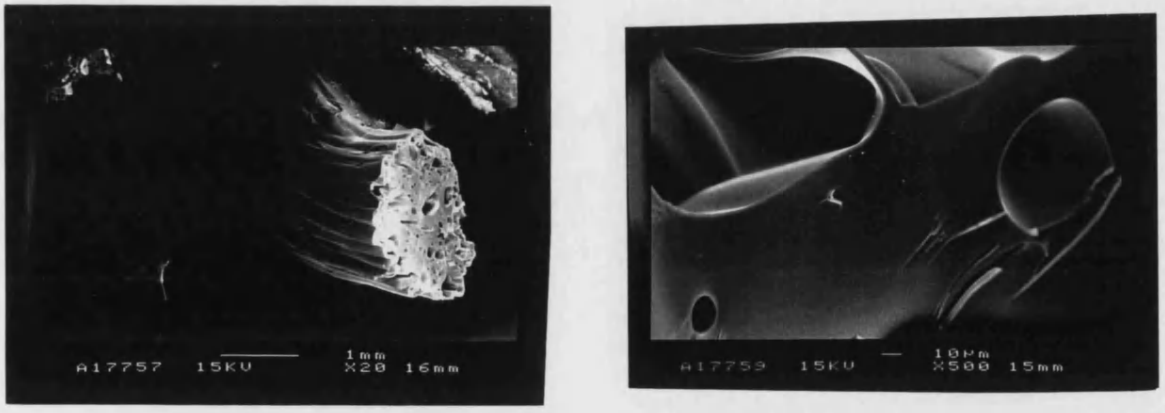
White solid strands of polymer were collected in the cold trap at 40°C and 300 bar. A study of the cross-sectional of a single strand was found to be porous (see figure 7.16a). At a higher magnification a pore was studied and this too had porous structure (see figure 7.16b).



(a) (b)

Figure 7.16 *poly Methylmethacrylate treated at 40°C and 300 bar in $scCO_2$ – Methylene Chloride system (a) x50, (b) x500 magnification.*

At 600 bar and same temperature the porous strand was replaced by hard solid and semi-porous structure. The surface had a glazed appearance and surface was smooth (see figures 7.17a and b).



(a) (b)

Figure 7.17 *poly Methylmethacrylate treated at 40°C and 600 bar in $scCO_2$ – Methylene Chloride system (a) x20, (b) x500 magnification.*

In this set of experiments at 60°C, a thin polymeric film was collected in a modified cold trap. The attaining of this film was a milestone in this project. It was a thin, brittle and bubble-filled film. Only a small section of the film has been photographed life size (see Figure 7.18). The overall film was prone to breakage.

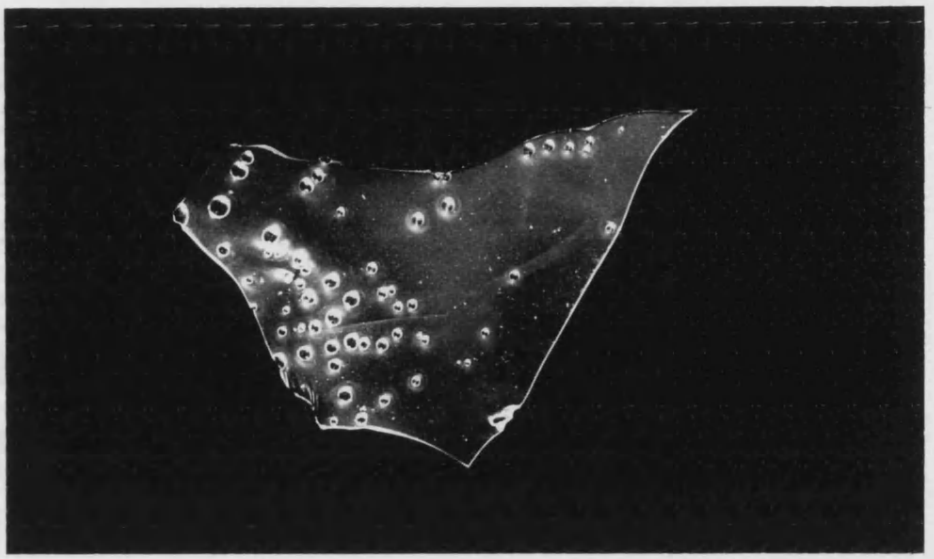


Figure 7.18 *poly Methylmethacrylate treated at 60°C and 300 bar in $scCO_2$ – Methylene Chloride system (life size, no magnification).*

When the pressure was doubled to 600 bar even thinner film was collected (see Figure 7.19). This polymeric film was less brittle and contained fewer air bubbles. A small section has been photographed life size.

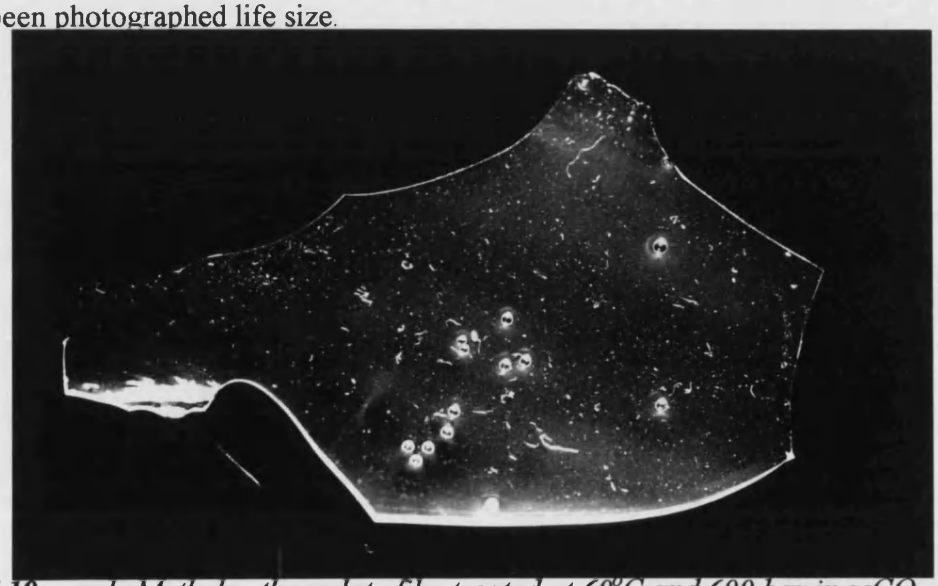


Figure 7.19 *poly Methylmethacrylate film treated at 60°C and 600 bar in $scCO_2$ – Methylene Chloride system (life size, no magnification)*

8. *Discussion and Conclusions*

In this chapter an in depth discussion is presented on the polymers' solubilities in $scCO_2$ system and in the $scCO_2$ – methylene chloride system. The effect of increasing pressure (and to some extent the temperature) will be discussed for each polymer in relation to density changes in supercritical carbon dioxide. The effect of chemical structure and molecular weight on solubility is also considered.

Scanning Electron Microscopy analysis of morphological changes over a range of temperature and pressure parameters is discussed and conclusions drawn on the suitability of particular polymers in the pharmaceutical drug delivery.

The potential uses of $scCO_2$ – methylene chloride based polymeric films will be assessed from the morphological point of view, since it was possible to produce both a porous and a non-porous film.

The economics of producing a polymeric film from a $scCO_2$ – Methylene Chloride system will be considered in relation to the environmental gain. The use of $scCO_2$ and $scCO_2$ – Methylene Chloride system in future pharmaceutical applications is also discussed.

8.1 Nature of Solvents

Carbon dioxide is a non-polar molecule of a molecular weight of 44.0. At ambient conditions it exists as a gas. There are 2 double covalent bonds in one carbon dioxide molecule. In theory "like should dissolve like" (Kurnik *et al* 1982 and Dobbs *et al* 1986) therefore what is a non-polar solvent should dissolve a non-polar solid. However in practise supercritical carbon dioxide dissolved some materials of polar type in addition to the non-polar molecules studied. The reason for this will be discussed later in this chapter.

Methylene chloride (dichloromethane) is a chlorinated hydrocarbon. In general chlorinated hydrocarbons tend to be good solvents for non-polar materials. However, the C-Cl bond in methylene chloride is polar enough to partially dissolve polar materials. Methylene chloride is a liquid at ambient conditions and it has excellent properties, including high solvency power, low boiling point (40°C) and that makes it an optimum process solvent in the manufacture of pharmaceutical products.

8.2 Nature of polymers and solubility

Both polar and non-polar polymers of different molecular weights were studied and this enabled conclusions to be made on solubility patterns. The nature of bonding in the polymers studied plays an important role in solubility in pure $scCO_2$ and in the $scCO_2$ – Methylene Chloride system. Polymer solubilities were also measured in pure Methylene chloride for a comparative purpose and these solubilities were found to be intermediate to those determined from $scCO_2$ and the $scCO_2$ – Methylene Chloride system. In addition to

the chemical structure considerations, the effect on solubility of pressure change and therefore density change of the solvent has been recorded and is discussed here.

8.2.1 poly ß Hydroxbuteric Acid

poly ß Hydroxbuteric Acid was found to be insoluble within the limits of detection (see table 6.3). This can be attributed to a number of reasons. poly ß Hydroxbuteric Acid is a high molecular weight polymer and it is a polar molecule that was subjected to a non-polar solvent, supercritical carbon dioxide. Considering general principle that, like dissolves like; it is understandable why non-polar carbon dioxide even in a supercritical state was not able to react with the polar molecule of ß Hydroxbuteric Acid (see Figure 8.1). Because of this overall principle, increasing temperature or pressure had no effect on the polymer. Hence no solute was collected in the cold trap. In addition poly ß Hydroxbuteric Acid was of high molecular weight and high molecular weight polymers tended not to react with pure $scCO_2$.

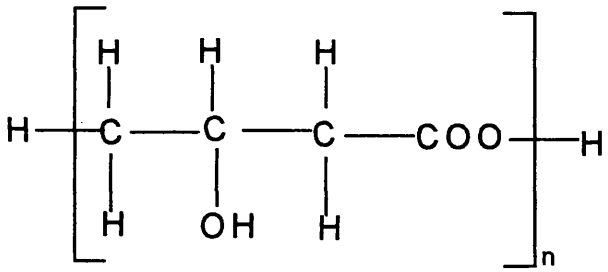


Figure 8.1 *ß Hydroxbuteric Acid monomer, Mol. Wt. = 104.11, where n ~ 5139*

poly ß Hydroxbuteric Acid was not studied at temperatures above 60°C and pressure above 600 bar because of the limitations of the experimental rig. Lack of sample availability

meant that this particular polymer could not be studied in a $scCO_2$ – Methylene Chlorides system, which would have shown its behaviour in the chlorinated co-solvent.

8.2.2 Hyroxypropyl Methylcellulose (HPMC)

HPMC was studied at pressures of 300 bar and 600 bar in $scCO_2$. It was found to be effectively insoluble at 300 bar across all temperatures. However at 600 bar the solubility was measurable. At 600 bar and 35°C solubility was found to be 0.0014 %(w/w); this increased to 0.0082 % (w/w) at 60°C (see Figure 6.2and Table 6.3). Following such a low solubility determination, HPMC was studied in a $scCO_2$ – Methylene Chloride system. The solubilities increased (see Figure 6.8 and Table 6.3) by 100 fold. At 60°C, solubility increased to 1.192 % w/w which was significant leap from 0.124 % w/w at 35°C in $scCO_2$ – Methylene Chloride system.

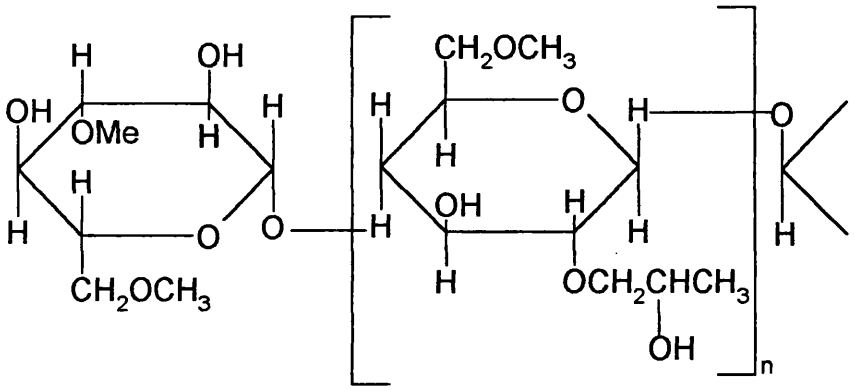


Figure 8.2 *HPMC molecule, Mol. Wt. = 22,000 where n ~ 100.*

The solubility trend in a co-solvent system is an indication that HPMC is perhaps a polar molecule (see Figure 8.2) and that is why it had low solubility in the pure $scCO_2$. However on a closer look at the molecule it is apparent that the atoms within this molecule are

joined by strong covalent forces, the separate molecules however are held together by weak Van der Waal's forces. These weak intermolecular forces permit the molecules to be separated in the presence of a chlorinated co-solvent. Although Van der Waal's forces are small between these molecules, the total Van der Waal's forces between the molecules of a large polymer like HPMC with many contacts can be very significant. In addition there is some hydrogen bonding (see Figure 8.4) between oxygen and hydrogen in this molecule. Basic chemistry tells us that hydrogen bonding results in exceptionally polar molecule with stronger intermolecular forces than usual, which can only be counteracted by polar solvent. Solubility is significantly higher in the co-solvent system than in a pure supercritical carbon dioxide because of the presence of the polar co-solvent, the methylene chloride.

8.2.3 poly Methylmethacrylate (PMMA)

PMMA was sparingly soluble in the $scCO_2$ system. It was least soluble at 35°C and 60°C. A bell shaped solubility profile was achieved, where maximum solubility was attained at 45°C for all pressure studied (see Figure 6.3). Solubility increased with temperature up to 45°C, following that solubility decreased with increasing temperature. This goes to explain that increasing the temperature doesn't warrant increasing solubility in the case of high molecular weight polymers. Increasing temperature of supercritical system reduces fluid density and the dielectric constant of the carbon dioxide, hence reducing the solvating power therein. When solubility was plotted against pressure (see Figure 6.4), solubility increased with increasing pressure. This was because as the pressure of the liquid carbon dioxide increased its vapour pressure and fluid density increased as well. This in itself would tend to increase solubility. In general solubility was less than 0.05% w/w $scCO_2$.

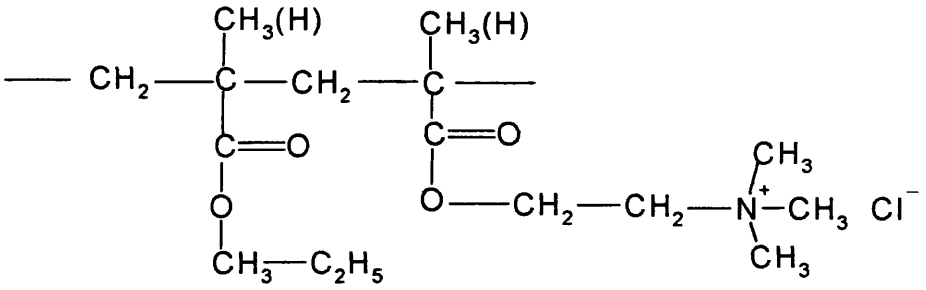


Figure 8.3 Methylmethacrylate Monomer (Mol. Wt. of PMMA =150,000)

This low solubility can be explained in terms of the chemical structure of PMMA (see Figure 8.3). PMMA has hydrogen bonding of two types, there is an O-H and a N-H bond (see Figure 8.4) in the monomer which resist carbon dioxide.

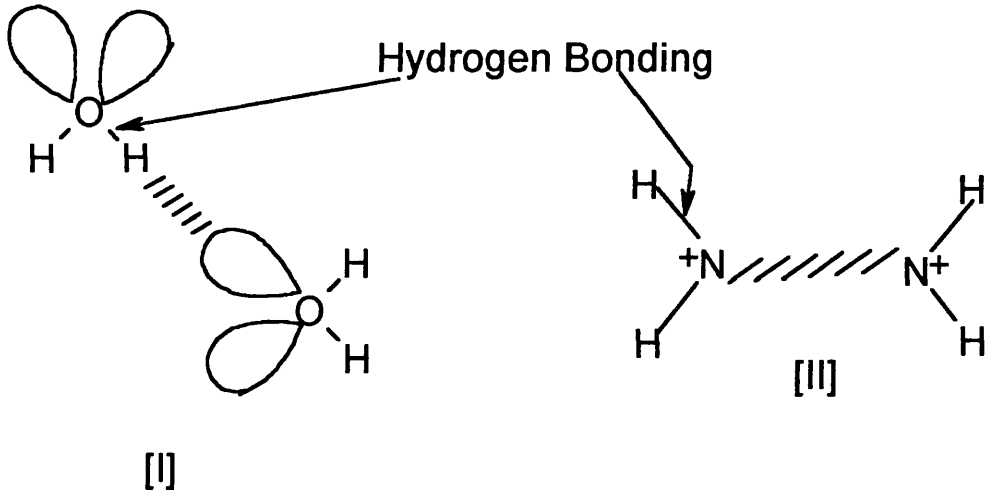


Figure 8.4 Examples of hydrogen bonding between [I] hydrogen/oxygen and [ii] nitrogen/hydrogen.

Both oxygen and nitrogen are strongly electronegative elements when they are bonded to hydrogen atom. A strong intermolecular force exists between molecules of PMMA and

this makes it hard for non-polar carbon dioxide to separate molecules even at high pressure and density.

In the co-solvent system, when solubility was plotted against temperature, a steady increase in solubility was observed at each pressure (see Figure 6.9). Solubility reached 2.11 % w/w when PMMA was reacted with $scCO_2$ – Methylene Chloride system at 40°C and 600 bar thus indicating that PMMA has some polarity, which is interacting with the co-solvent to give a 75 fold increase. Solubility reached some 8.21 % w/w at 60°C and 600 bar. This exceptionally high solubility can be attributed to the interaction of C-Cl bond in Methylene Chloride, which is a polar bond. However, C-Cl is not polar enough to effect major changes, nevertheless it does have appreciable effect on solubility in solubilising PMMA polymer. For PMMA solubility generally increased by just over 100 fold in the presence of chlorinated solvent but at 60°C and 600 bar there was approximately a 500 fold increase in solubility.

8.2.4 poly D, L lactide (Mol. wt. 9,000)

poly D, L lactide had significantly higher solubility in comparison to high molecular weight polar molecules such as PMMA, poly ß Hydroxbuteric Acid and HPMC in pure $scCO_2$ system, although not as soluble as poly D, L lactide of a molecular weight of 2,000. Solubilities were less than 0.5 % w/w. The solubility increased with increasing temperature with this low molecular weight polymer. The solubility at various temperatures at 600 bar (see Figure 6.5) was significantly greater from those at 500, 400 and 300 bar and similar temperatures and this is because it is possible that $scCO_2$ was acting as vapour, below 600 bar. When solubility was plotted against pressure (see Figure

6.6) there was a linear increase and the solubility profiles were parallel to each other. It can be said that increasing pressure has more pronounced effect in increasing solubility at a set temperature because as pressure increased so did the density and the dielectric constant of carbon dioxide (Michel *et al.* 1933). The effect of increasing pressure results in higher solubility for low molecular weight polymers like poly D, L lactide. This was reflected in solubility data in the Table 6.3. In terms of the chemical structure poly D, L lactide (see Figure 8.5) is covalently bonded molecule with weak Van der Waal's forces that were broken down with likewise solvent, the carbon dioxide. poly D, L lactide has no hydrogen bonding to oppose the solvent power of $scCO_2$.

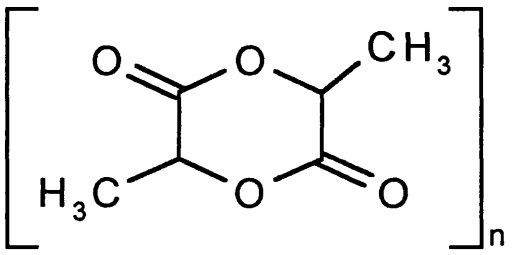


Figure 8.5 *D, L lactide Momoner, (Mol. Wt.of poly D,L lactide = 9000, where n ~ 63)*

In the $scCO_2$ – Methylene Chloride system, the effect of increasing temperature and pressure meant that solubilities increased by approximately 20 fold in the co-solvent (see figures 6.12 and 6.13) system. An interesting pattern emerged whereby an increase in solubility of some 50-90 fold was measured at 300 bar at temperature range of 35-60°C in relation to solubility in $scCO_2$. However at 600 bar the solubility increase dropped to approximately 20 fold in relation to solubility in $scCO_2$. It can be said that the co-solvent system at 300 bar is more effective than at 600 bar in relation to solubility in $scCO_2$.

8.2.5 poly D, L lactide (Mol. wt. 2,000)

poly D, L lactide of molecular weight of 2,000 (see Figure 8.5) was the most soluble of the range studied in the pure $scCO_2$ system. Studying a high and a low molecular weight poly D, L lactide has illustrated that the lower the molecular weight of poly D, L lactide the more soluble it is in the $scCO_2$ system. poly D, L lactide was most soluble at 45°C and 600 bar amongst the polymers studied, at 60°C it gave yet the highest solubility of 1.01 % w/w in the pure $scCO_2$ system. It is possible that this polymer need not be studied in the $scCO_2$ – Methylene Chloride system since under carefully controlled conditions it has the potential of having sufficient solubility in pure $scCO_2$. It was possible to produce 1.01% w/wt of polymer with 40 dm^3 of carbon dioxide that is 72.6 g of carbon dioxide.

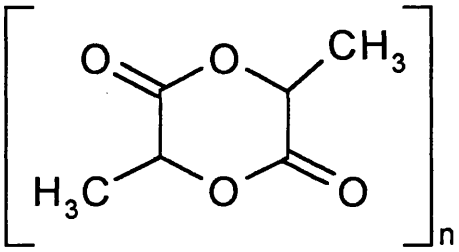


Figure 8.6 *D, L lactide Monomer, (Mol. Wt.of poly D, L lactide = 2,000 where n ~ 14)*

8.2.6. poly D, L lactide-co-glycolide (Mol. Wt. 3,000)

poly D, L lactide-co-glycolide displayed similar behaviour to that of poly D, L lactide (Mol.Wt. = 9,000) but solubilities were 100 fold lower in the pure $scCO_2$. Solubility increased with increasing temperature and pressure, the profile at 600 bar stood apart from

the other pressures (see figure 6.11) when solubility was plotted against the temperature. This is indicative of pressure above 600 bar having significant effect on the solubility of poly D, L lactide-co-glycolide. Here the hypothesis of low molecular weight giving high solubility ceases to work as poly D, L lactide-co-glycolide is a low molecular weight polymer. The lactide and glycolide molecules in this polymer are highly polar hence little, if any, interaction with carbon dioxide was observed.

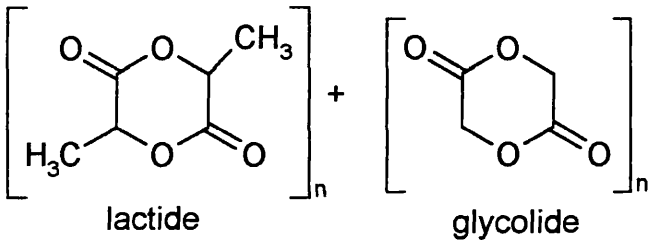


Figure 8.7 D,L-lactide and glycolide molecule, 50:50 ratio, Mw=3,000

In the $scCO_2$ – Methylene Chloride system, the effect of co-solvent results in solubility increase by 500 fold at 45°C and 600 bar and by a 1000 fold at 300 bar in relation to solubility in $scCO_2$ at same conditions. This is a significant increase from being barely soluble in supercritical carbon dioxide to being highly soluble polymer in this study. Here methylene chloride in conjunction with supercritical carbon dioxide has displayed its powerful solvating effect.

8.3 *Morphological Changes by Scanning Electron Microscopy*

Scanning Electron Microscopy (SEM) has been used to study the external morphology of the polymers before and after subjecting the polymer to $scCO_2$ and the $scCO_2$ – Methylene Chloride system. Morphological changes recorded gave significant information about the potential uses of various polymers studied.

The surfaces of poly Methylmethacrylate (PMMA), poly D,L lactide (Mol.wt.= 2,000) poly D,L lactide (Mol.wt. 9,000) and poly D,L lactide-co-glycolide were studied over some pressure and temperature parameters. Discussion of the results presented in Chapter 7 is given here.

8.3.1 SEM study: poly D, L lactide (Mol. Wt.= 2,000)

poly D, L lactide of low molecular weight started off as a white highly electrostatic powder that on contacting with $scCO_2$ at 45°C over a pressure of 600 bar became a fold bearing surface (see Figure 7.2) and at 60°C a inflated bubble-like surface was formed. This latter structure shown in Figure 7.3 has a potential of forming a defined polymeric film at carefully controlled conditions. It was the most soluble polymer studied. It is not essential to use the $scCO_2$ – Methylene Chloride system to produce a defined film. However if $scCO_2$ – Methylene Chloride system is used much lower pressure can be adapted to achieve higher solubility.

8.3.2 SEM study: poly D, L lactide (Mol. Wt.= 9,000)

poly D, L lactide of higher molecular weight also started off as a white static powder, however on contacting with $scCO_2$ at 35°C over a pressure of 600 bar it become a gelatinous network (Figure 7.5) of strands which has a potential of housing drug in its physical structure and this drug could be sealed in by subjecting the drug/polymer matrix to a temperature of 45°C. At 45°C a continuous fold structure is seen (Figure 7.6). Since this polymer is biodegradable it has the potential to form an ideal drug delivery product as a slow release subcutaneous injection.

In a $scCO_2$ – Methylene Chloride system colourless gel-like droplets were collected in the cold trap. On a higher magnification these droplets were found to have entwined plaits (see Figure 7.11) running through the sample under test. On contacting with $scCO_2$ – Methylene Chloride at 45°C and 600 bar uninterrupted smooth folds were observed (see Figure 7.12). This structure does not display potential for controlled release since there was no uniformity in the pattern.

8.3.3 SEM study: poly D, L lactide-co-glycolide (Mol. Wt.= 3,000)

poly D,L lactide-co-glycolide a low molecular weight polymer was not tested in pure $scCO_2$ due to the accidental loss of those samples. In a co-solvent system poly D, L lactide-co-glycolide came up as gelatinous and colourless polymer. In its untreated state it was a white solid powder and extremely electrostatic (see Figure 7.13a and b). On reacting with $scCO_2$ – Methylene Chloride at 35°C and 600 bar, those isolated powder particles formed a colourless solid clump, which bore irregular folds (see Figure 7.14a and b). On

reacting at a temperature of 45°C, these folds flattened to fine striations. No potential uses can be envisaged as far as poly D, L lactide-co-glycolide is concerned at low temperature. However, the flattened surface is promising in that it could be used as film; but carefully controlled experiments need to carried out to ascertain the optimum conditions for producing a viable film from this polymer.

8.3.4 SEM study: poly Methylmethacrylate (PMMA)

Untreated PMMA existed as a white spherical granule with an uneven surface (see Figure 7.7). In the $scCO_2$ it remained a white solid with undulated surface. White solid was collected in the cold trap. This was found to be highly porous (see Figure 7.9). These pores reduced in size when the temperature was increased by 20°C (see Figure 7.10). This is a perfect example of pore size being controlled by the temperature or pressure parameters in the supercritical fluid technique. Further investigation could determine the parameters needed to produce a suitable pore size for incorporating drug into the pores. In the $scCO_2$ – Methylene chloride system large pore sizes were obtained at 40°C and 300 bar. This is at half the pressure used in pure $scCO_2$. At 600 bar in a co-solvent system no pores were observed.

8.3.4.1 SEM study: Polymeric Film from PMMA.

In the $scCO_2$ – Methylene Chloride system defined polymeric films were produced at 300 and 600 bar, at a set temperature of 60°C. A coherent film (see Figure 7.18) was successfully formed at 300 bar but this did contain large pores. However at 600 bar the pores are practically non-existent (see Figure 7.19). This is a powerful evidence for the

successful production of a polymeric film using the $scCO_2$ – Methylene chloride system. Further work is necessary for characterisation of the polymeric films obtained. A polymeric film should have the properties listed in section 2.6.2. To fine tune films produced in this study, further work at a range of pressures and temperatures in the $scCO_2$ – Methylene Chloride system is required. Porous films have the potential to be used as a controlled release coating on tablets whilst non-porous could be used to coat tablets to dissolve in a specific environment.

8.4 Economics of the process

The results obtained have given valuable information on the behaviour of pharmaceutically important polymers in pure $scCO_2$ and in the $scCO_2$ – Methylene Chloride. The solubility rig costs are tabulated in the Appendix II to give you an idea of initial cost involved. A pilot size rig cost approximately £15,000 and these included the fittings, tubing and equilibrium cell amongst others. The consumables included Carbon dioxide and Chemicals, the chemicals totalled £1,700. The usage cost of liquid CO_2 amounted to £32 per month, i.e. 4 x 18m^3 cylinders. A maximum of 0.04m^3 of carbon dioxide was used to solubilise and collect 0.74g of poly D, L lactide. This means that 351g of poly D, L lactide can be solubilised from one carbon dioxide cylinder at a cost of £8 for the liquid CO_2. This polymer is sufficient to coat more than 2 batches of 10,000 tablets since coating only form 2.5% w/w of a typical tablet weight of 0.5g. Methods of contacting tablets with the solubilised polymer/s need to be developed in order to coat successfully. This will add significantly to cost.

From the economic perspective the environmental benefits are that supercritical carbon dioxide is a fast evaporating solvent which means that no extra expenses need to be considered to overcome the problem of drying. It is non-corrosive which means that in a supercritical state it does not corrode the equilibrium cell unlike supercritical water that will corrode any stainless steel reaction cell within 2 hours (Smith RM *et al* 1996). Furthermore, carbon dioxide has low toxicity, which means only high concentrations of carbon dioxide can lead to asphyxiation. This is reflected in its very high thresh-hold limit value (TLV) of 5000ppm for carbon dioxide. This TLV is 10-100 times higher than nearly all other coating solvents (Donohue 1996). For example TLVs of some solvents are:

- toluene (100ppm),
- hexane (50ppm),
- ethyl acetate (400ppm)
- methylene chloride (400ppm).

It is therefore apparent from this, that methylene chloride and carbon dioxide are safe for usage hence no expense is necessary to make the work place safe from toxicity of carbon dioxide or methylene chloride. Carbon dioxide is non-flammable whilst fast evaporating solvents are typically highly flammable with low explosive limits of 1-2%. Finally, whilst fast evaporating solvents may generate odour to which workers can be exposed, carbon dioxide is odourless. This means no extra cost will be incurred to eliminate odour in the work place. Carbon dioxide's release into atmosphere and its impact on global warming can now be questioned. The answer to this is that the overall environmental effect of releasing carbon dioxide when compared to conventional solvent systems is less. It must be borne in mind that organic solvents discharged into the environment from conventional solvent systems eventually oxidise in the air to produce carbon mono-oxide and carbon dioxide. Each kilogram of solvent emission from conventional spray system produces

from 2.3 to 3 kg of new carbon dioxide. Moreover if the VOC emissions from spray coatings are incinerated to meet VOC regulation, the natural gas used as fuel for the incinerator can generate up to 18 kg of new carbon dioxide per kilogram of organic solvent emission (Nielsen *et al* 1990). Therefore it makes sense to use supercritical carbon dioxide and also explore the possibility of modifying rig to accommodate the recycling of the carbon dioxide which will be a more cost-effective method of reducing global warming. In terms of using a small percentage of co-solvent (2.5% v/v of carbon dioxide) only a small quantity of the co-solvent will be released into the atmosphere. This reduction in the emissions of VOCs will help minimise production of carbon dioxide in the environment.

The second issue related to economics of the process is the production of a polymeric film. It is envisaged that adhesion of a polymeric film to the tablet surface will not be a problem since solubilised polymer can be delivered to the tablet surface in a 'coating pan' at a controlled pressure. A diagrammatic representation of the mechanism of binding and

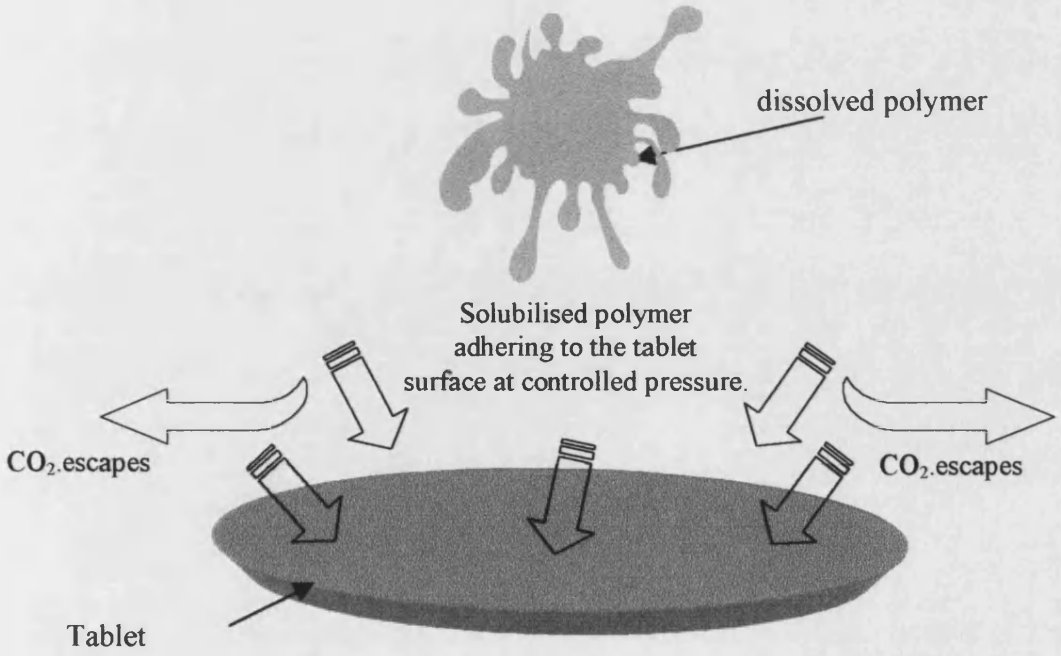


***Figure 8.8** showing how a polymer will deposit on the tablet surface.*

solidifying is shown in the figure 8.8 whereby a solubilised polymer spreads across a tablet at high pressure and upon dropping the pressure the polymeric film adheres to the tablet surface by the vacuum created between the surface and the polymer as carbon dioxide gas escapes into the carbon dioxide rich region, the air. It is not yet known whether a polymeric film could be de-bossed with identification label upon bonding to tablet surface.

8.5 Principal Conclusions.

- The usage of pure $scCO_2$ as a solvent has shown the potential to dissolve some pharmaceutically significant polymers at high pressure which can precipitate out of solution by controlling of conditions and allow CO_2 to escape into the atmosphere or be recycled by recompression.

- Increasing pressure increases density and dielectric constant of carbon dioxide and this leads to increased solvating power. Increasing temperature has two effects; (1) decreases density and dielectric constant leading to decreased solvating power of carbon dioxide, (2) increases vapour pressure of carbon dioxide thus increasing solvating power. At lower pressures an increase in temperature has larger effect on reducing the density of supercritical carbon dioxide than at higher pressures.

- The pure $scCO_2$ has shown its suitability for low molecular weight non-polar polymers such as poly D, L lactide. With low molecular weight non-polar polymers a linear relationship was observed with increasing pressure and temperature. This applied to poly D, L lactide and to some extent to poly D, L lactide-co-glycolide.

- Carbon dioxide is a non-polar covalently bonded molecule therefore solubility of high molecular weight polar polymers such as PMMA and HPMC was low. In the case of high molecular weight polar polymers of pharmaceutical interest, solubility increased with increasing pressure, although not significantly as the polar molecules were not interacting with the non-polar carbon dioxide. An increase in pressure has the effect of forcing the molecules closer together, thus increasing density and solvating powers of

the CO_2. Increasing temperature at a set pressure had a different effect on polar polymers of high molecular weight. HPMC and PMMA displayed increasing solubility with increasing temperature up to a maximum. Following this a decrease in solubility was observed, this is because the density of carbon dioxide increases rapidly up to approximately 200 bar above this pressure the rate of increase slows down as the density tends to a maximum (Michel *et al* 1935).

- In the co-solvent system solubilities increased by more than 2 orders of magnitude in relation to pure $scCO_2$ for high molecular weight polar polymers. This is an indication that polymer for coating applications ought to be subjected to $scCO_2$ – Methylene Chloride system at various temperature and pressures to determine maximum solubility. The combined effect of $scCO_2$ and compressed methylene chloride enhanced the solubility of the polymers of polar nature. In low molecular weight non-polar molecules solubility increased by approximately 2 orders of magnitude in relation to pure $scCO_2$.

- Scanning electron microscopy revealed that polymer surface changed when subjected to different temperature and pressure regimes in pure $scCO_2$ and in the $scCO_2$-*Methylene Chloride* system. It showed that porosity may be controlled by fine tuning pressure and temperature. It was found in some cases that the porous structure present at 300 bar in $scCO_2$-*Methylene Chloride* system disappeared when the same polymer was subjected to double the pressure. Therefore this porosity control could be a useful tool in developing a controlled release coating. The non-porous structure, can be made into a functional coating that is site specific by making it pH dependent.

- Polymeric films were collected from PMMA in the *$scCO_2$-Methylene Chloride* system and demonstrates the potential of film production using supercritical fluid technology.

- Overall, supercritical fluid technology has shown the potential of being used as an environmentally friendly process for defined coatings. It has potential in controlled release applications as a controlled release film on a tablet. It would be particularly suitable for those drugs, which may not be stable in traditional solvents.

8.6 Future Work

- To validate carbon dioxide a solvent for specialised polymer coating, further work is required in determining raw data at a range of pressures and temperatures with the support of SEM. This would enable fine-tuning of pressure and temperature parameters for each polymer. The determination of solubility could be aided by developing a solubility-predicting model. At present solubility in some cases can be modelled using the Cubic Equations of the State, which include the Peng-Robinson Equation of the State and the Soave Redlich Kwong Equations of the State. There is also a software package called the UNIFAC method for predicting solubility. There are drawbacks in each of these, for example the Cubic Equations of State can only be used to calculate properties of a pure material. Peng-Robinson Equation of the State and the Soave Redlich Kwong Equations of the State can only be used to predict the solubility of low molecular weight, non-polar materials such as naphthalene. The UNIFAC method only estimates physical properties of a compound on the functional groups making up that compound and hence it is intrinsically less reliable. Price *et al*

have used it for some non- pharmaceutical polymers in 1987. This is indicative of a gap in predictive modelling for solubility and hence further research needs to be carried out in an attempt to develop models for solubility of polymers of pharmaceutical interests.

- It is recommended that in future poly D, L lactide is studied at a range of conditions and in a $scCO_2$ in an attempt to produce polymeric film since it was highly soluble in the pure $scCO_2$. PMMA ought to be studied in a co-solvent system at a range of conditions for porosity control. HPMC need not be soulibilised in supercritical carbon dioxide or in $scCO_2$-Methylene Chloride system, since it is water-soluble and it is used in coatings at present.

- Supercritical carbon dioxide could be used as an anti-solvent, instead of acting as a solvent to solubilise coating polymer. The anti-solvent action would require that polymer is dissolved in an organic solvent and coating applied to tablets prior to contacting supercritical carbon dioxide with coated tablets at a controlled pressure in an attempt to carry away moisture. As the pressure is dropped the supercritical carbon dioxide containing organic solvent will precipitate out of solution thus elevating the problem of residual organic solvents.

- On a technical issue it is recommended that a dynamic flow type rig is constructed using a ½" O.D, 316 Stainless Steel tubing since enormous problems of blockage were encountered with ¼" O.D tubing.

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Appendix I

A1. Mechanical Design and Specifications of the Equilibrium Cell *(courtesy of A. Broadbent 1997)*

The equilibrium cell was machined from 316 stainless. A 2 inch steel bar was cut to a length of 400mm. The end caps were machined from a 5 inches diameter. The equilibrium cell was inspected and approved by National Vulcan for its pressure tolerance. All tolerances were +/- 0.1 mm, except where tighter tolerances are specified on the drawings. The tolerances on angles were +/- 0.5°, except where tighter tolerances are specified on the drawings. The fit between the end connectors and the equilibrium cell is critical, as the integrity of the o-ring seals depend on this: the surface finishes are to be 0.4 μm Ra, or better on the mating surfaces between the end connector and the equilibrium cell. The tolerance on the end connector is to be f8, as defined in B.S.4500, i.e. -16 to - 43 μm. (0.707 - 0.708"). The tolerance on the equilibrium cell is to be H9, as defined in B.S.4500, i.e. 0 to +43 μm. (0.709 -0.710"). The dimensions for the grooves on the end connectors are critical. These must be made within the specification on the drawing. The $^3/_8$" tube section on the end connectors are to take standard Sno-Trik reducing unions, to accept $^1/_4$" thick walled tubing.

A1.1 Assembly Drawings.

A1.1.1 Design of the Equilibrium Cell

The equilibrium cell was based on the specifications set out in Juvinal (1983), Shigley (1986) and BS 5500. The design and construction was approved by National Vulcan Engineering Insurance Group Ltd. (Manchester, U.K.), and the equilibrium cell was hydrostatically tested to 1250 bar by Baskerville Ltd. (Manchester, U.K.). The cell was machined from 2" (50 mm), 316 stainless steel bar, to give an internal diameter of 18 mm. The internal length was 350 mm, giving a total volume of 89,000 mm^3 (89 cm^3).

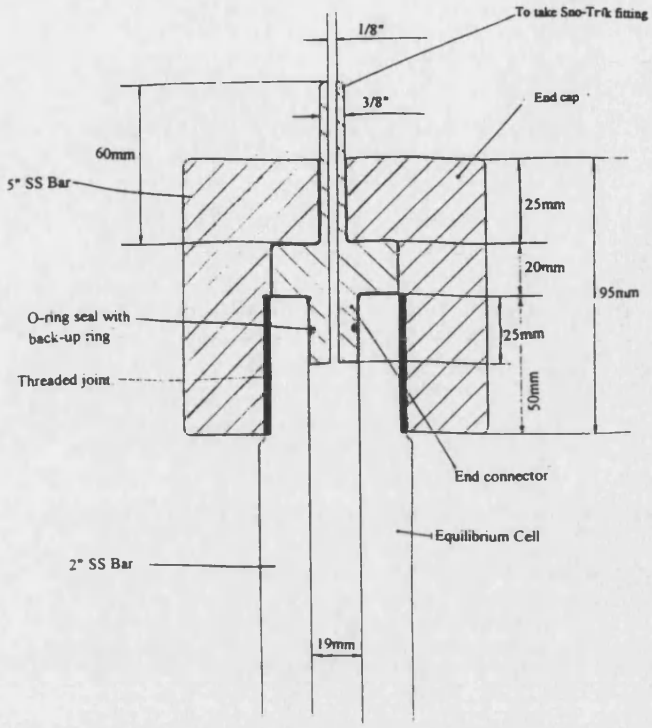
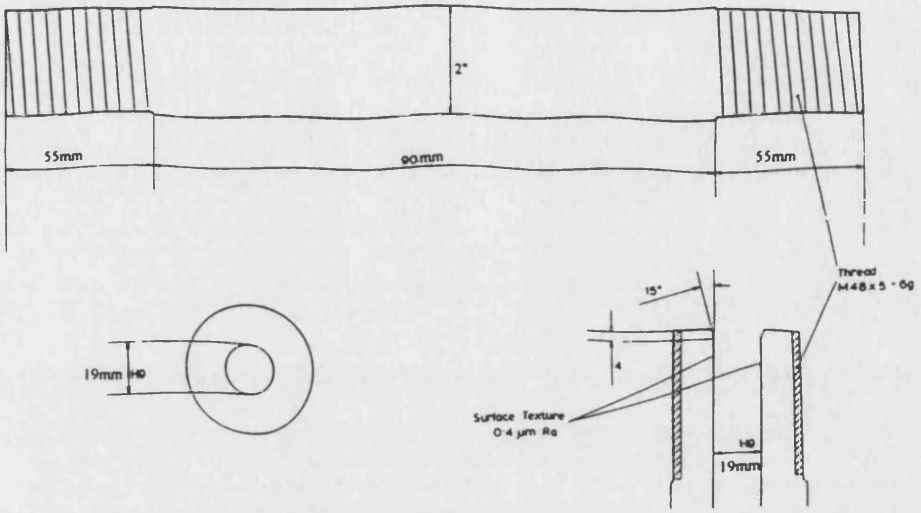
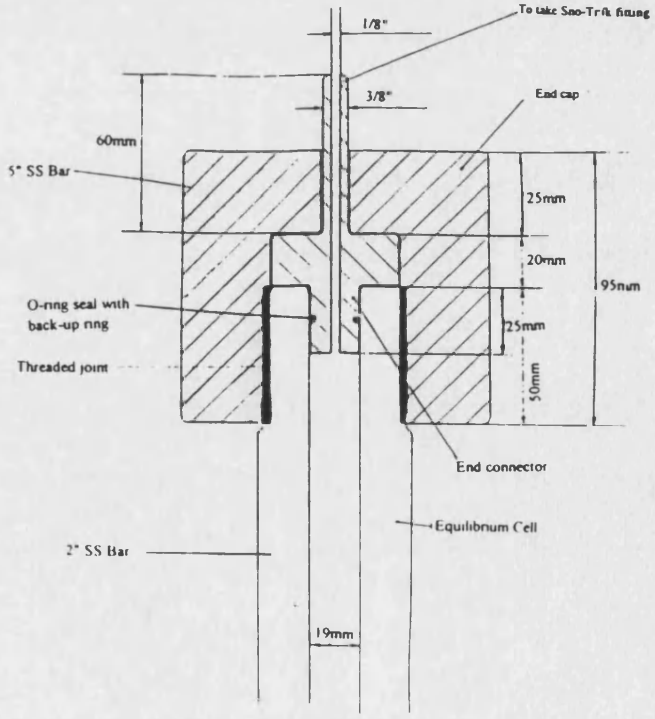


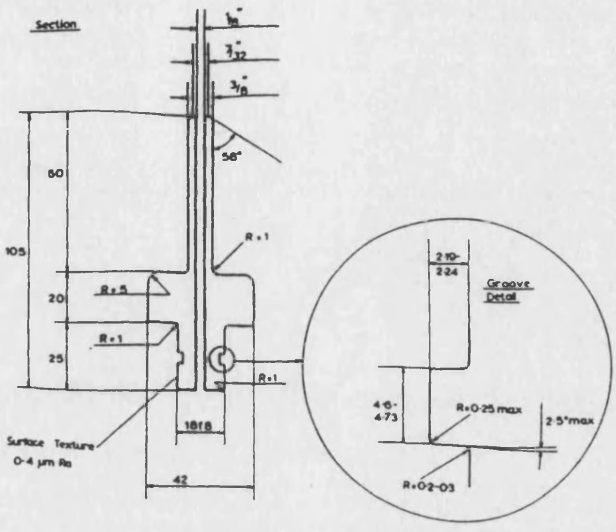
Figure A4 *Equilibrium cell end fittings (courtesy of A. Broadbent 1997).*

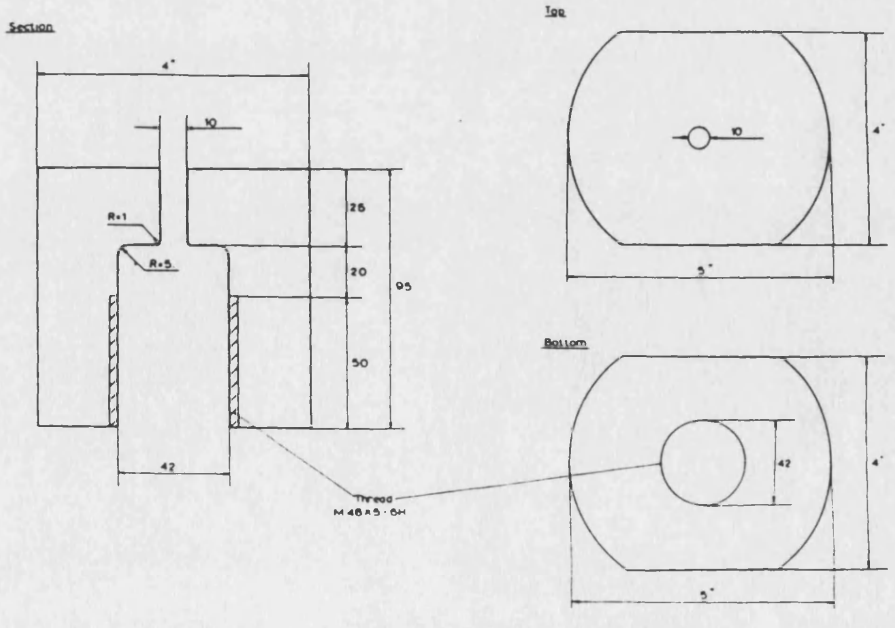
The equilibrium cell end fittings are shown in Figure A4. The end connectors were machined to take standard Autoclave Engineers unions. Viton rubber O-rings and PTFE backup rings were used to give a pressure tight seal between the cell and the end connectors.





N B All the components were machined from 316 Stainless Steel


Section
60
105
20
25
R=1
R=5
R=1
R=1
56°
18f8
42
Surface Texture
0·4 μm Ra
2·10-
2·24
Groove
Detail
4·6-
4·73
R=0·25 max
2·5°max
R=02-03


Section
4"
10
R=1
R=5
25
20
50
95
42
Thread
M48x5·6H
Top
10
4"
5"
Bottom
42
4"
5"

A1.2 Design Calculations.

The equilibrium cell was designed with following calculations in mind. The wall thickness, and the thread load stress calculations were used to machine the equilibrium cell however, the end caps and end connectors were modelled using "Ansys", a finite element analysis package, in conjunction with the School of Mechanical Engineering. Manufacturing drawings of the different components were produced including all dimensions and tolerances (see below).

A1.2.1 Material Specifications.

Material of construction,	316 Stainless Steel,
Design pressure	P = 690 bara, (69 Nmm^{-2}, 10,000psi)
Design temperature	T = 250°C
Design stress of steel (BS 5500)	σ_d = 103 Nmm^{-2}

A1.2.2 Dimensions of the Equilibrium Cell.

The equilibrium cell was cut from 2" (50 mm) bar, giving a wall thickness of 16 mm, and internal diameter of 18mm. The thread was taken into account, as this reduces the wall thickness of the cell at the ends. The thread size selected was M48 x 5. The minor diameter of this thread was 42 mm, therefore the least wall thickness will be 12 mm, hence greater than the minimum permitted (see A1.2.3).

d_i = Internal diameter = 18 mm

l_i = Internal length = 350 mm

A1.2.3 Wall Thickness

Applying Lame's equations:

$$-\sigma_r = A - \frac{B}{d^2} \qquad (1)$$

$$\sigma_\vartheta = A + \frac{B}{d^2} \qquad (2)$$

Where:

σ_r = radial stress, Nmm^{-2}

σ_θ = hoop stress, Nmm^{-2}

d = diameter, mm

A, B, = constants of integration.

For thick walled pressure vessels, where $d = d_i$:

σ_r = P = 69 Nmm^{-2}

σ_θ = max permitted stress σ_d 103 Nmm^{-2}

Therefore equations (1) and(2) become:

$$-69 = A - \frac{B}{18^2} \qquad (3)$$

$$103 = A + \frac{B}{18^2} \qquad (4)$$

(4) - (3):

$$172 = \frac{2B}{18^2}$$

$B = 27864\ N$

Substitute B into (4):

$$A = 103 - \frac{27864}{18^2}$$

$A = 17\ Nmm^{-2}$

When d = minimum outer diameter, d_{om}, $\sigma_r = 0\ Nmm^{-2}$, therefore (1) becomes:

$$0 = A - \frac{B}{d_{om}^2} \qquad (5)$$

Substitute A and B into (5) to give:

$$d_{om}^2 = 1639$$

$$d_{om} = 40.5\ mm$$

The minimum wall thickness, t_m, can now be calculated:

$$t_m = \frac{d_{om} - d_i}{2}$$

$$t_m = \frac{40.5 - 18}{2}$$

$$t_m = 11.25\ mm$$

A1.2.4 End Sections.

There are dangers that the end sections may fail in one of two ways: the threads may strip, or the end may fracture at the base of the threads.

The force, F, exerted on the end sections due to the pressure within the vessel may be calculated using:

$$P = \frac{F}{A}$$ where: A = Cross - sectional area, $= \frac{\pi d_i^2}{4}$

$= 254.5 \text{ mm}^2$

$F = P * A$

$= 69 * 254.5$

$= 17561 \text{ N}$

A1.2.5 Thread Stress.

The thread selected was M48 x 5. The major diameter d_m of this thread is 48 mm, and the minor or root diameter d_r is 42 mm (Shigley, 1986).
From Juvinal (1983) thread bearing stress, σ_t, is calculated using:

$$\sigma_t = \frac{4F}{\pi\left(d_m^2 - d_r^2\right) n}$$ Where n = no of threads in contact, = 10

$$\sigma_t = \frac{4 * 17561}{\pi\left(48^2 - 42^2\right) 10}$$

$\sigma_t = 4.2 \text{ Nmm}^{-2}$

This is well below the design stress.

A1.2.5 End Fracture.

There is a danger that fracture may occur at the base of the threads, at the point where the cross-sectional area of steel is least. This will be across the root diameter of the thread. The stress area to be considered, A_t, is the area of the annulus with inner diameter d_i and outer diameter d_r.

$$A_t = \frac{\pi\left(d_r^2 - d_i^2\right)}{4}$$

$$A_t = \frac{\pi\left(42^2 - 18^2\right)}{4}$$

$$A_t = 1130 \text{ mm}$$

The stress in this area, σ_f, is found using:

$$\sigma_f = \frac{F}{A}$$

$$\sigma_f = \frac{17561}{1130}$$

$$\sigma_f = 15.6 \text{ Nmm}^{-2}$$

This is well below the design stress.

A1.2.6 Ansys Models

Ansys is a powerful finite element analysis package used by engineers for a variety of tasks including the study of structures under load. It is available on the University of Bath computer network under an educational licence agreement. The following analysis was carried out by Mr. W. R. Taylor and Mr A Broadbent, School of Mechanical Engineering.

Ansys was used to model the cell end caps, and end connectors, as no straightforward design protocol was available. Ansys requires the following to be specified by the user:

- The size and shape of the object. The shapes of both objects were defined by specifying key points, and then joining them up with lines to give two-dimensional shapes. These were then rotated about a specified axis to form the desired three dimensional shape.
- The Young's modulus of the material under consideration. The Young's modulus for 316 stainless steel at 250°C was taken to be 180E-9 Nm^{-2}.
- The position, direction and magnitude of the force acting on the object. The force acting on the components was calculated from the maximum pressure and the cross sectional area of the cell.
- The point/s at which the object is restrained. The points of restraint were known from the general assembly drawing.

Ansys software divides the shape up into many small elements. It calculates the stress distribution within the object by considering the interactions between the elements caused by the applied force and the restraint. The accuracy of the model depends on the number and size of the elements, and the user specifies this. The results show stress distributions in two-dimensional shape.

Ansys Results for the End Cap.

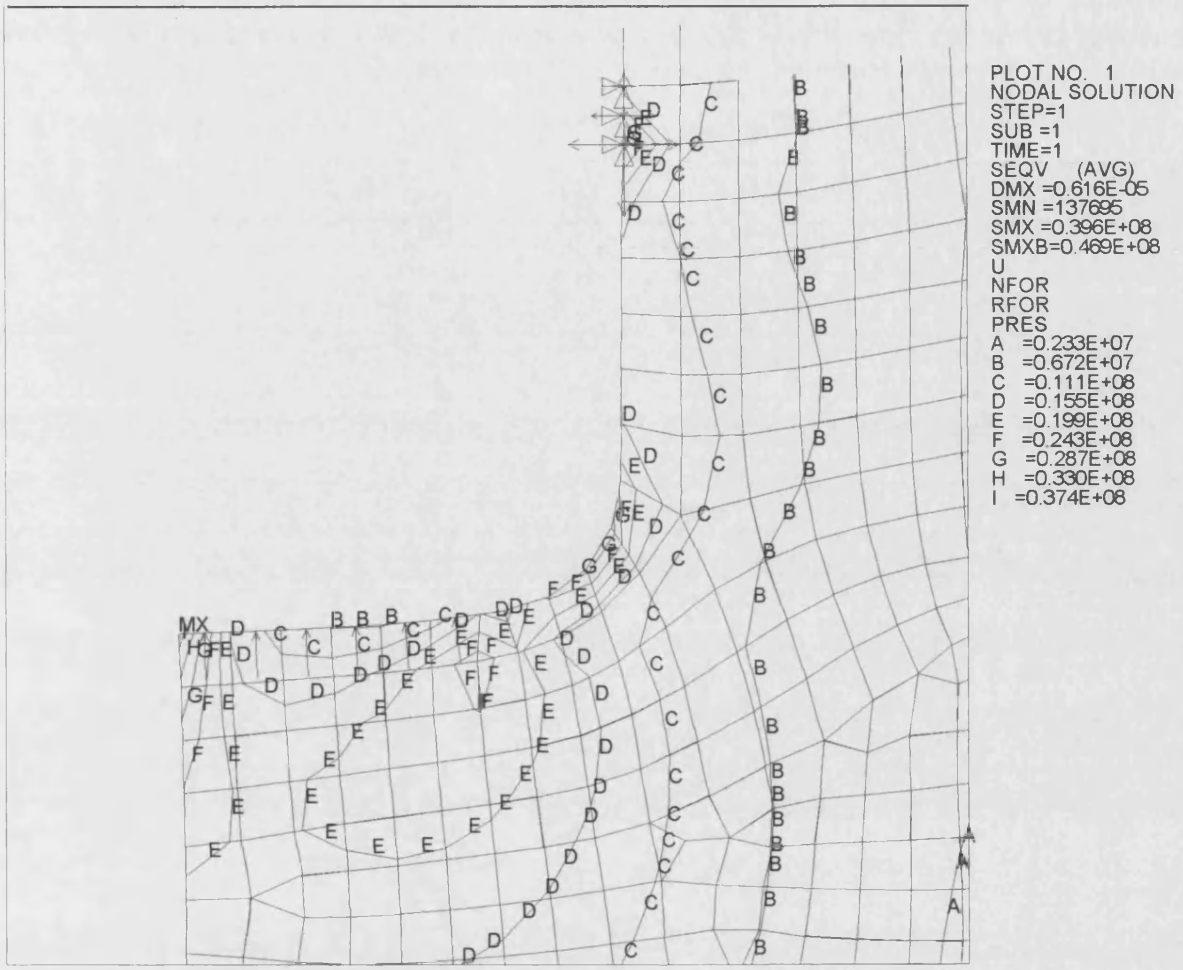


Figure A5. END CAP STRESS CONCENTRATIONS.

From the stress data on the right side of Figure A5 it can be seen there is a large stress concentration up to 0.287E8 Nm^{-2} in the internal corner, G. This is however, below the design stress of the steel, 1.03E8 Nm^{-2}. A high stress concentration was expected on this internal corner, and hence the corner was designed with a 5mm radius, to reduce the stress. The Ansys model calculated that the largest stress concentration occurs at the points labelled MX and H in the bottom left hand corner. This was due to the load being applied along the whole of that length. The end caps have been made with these corners rounded off eliminating this problem.

The points of restraint are shown by the arrows ⊳ at the top of the picture, and these correspond to the position of the thread. The stresses calculated at these points are far higher than the thread stress calculated previously. This is because the model did not take into account the geometry of the threads.

Ansys Results for the End Connector.

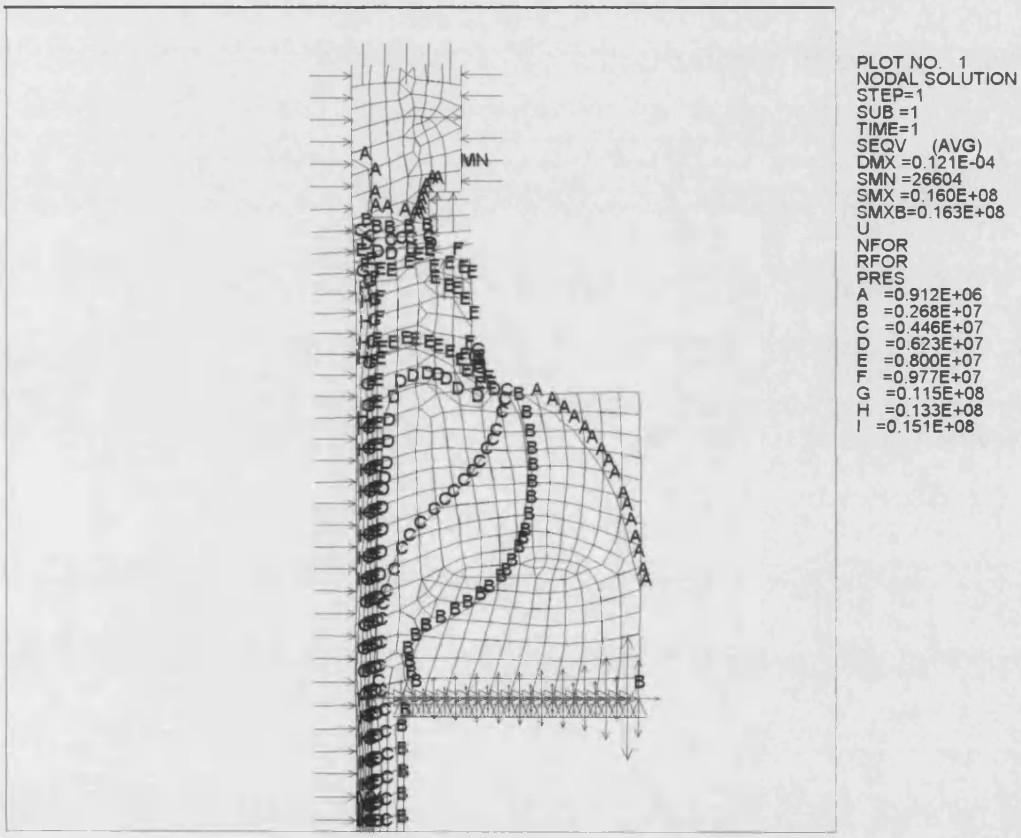


Figure A6. End Connector Stress Analysis

From the stress data of Figure A6 From it can be seen that the largest calculated stresses occurred along the left-hand side of the picture, i.e. inside the hole through the end connector. The minimum wall thickness permitted for the thin tubular section of the end connector was calculated using Lame's equations, as described previously. This was

considerably less than the specified wall thickness, and therefore the model was presumed to be inaccurate at that part.

High stress was expected to occur at the corner just below the groove for the O-ring but the model gave a stress concentration of 0.115E8 Nm^{-2} at that point, which is well below the design stress of 1.03E8 Nm^{-2}.

Appendix II

AII.I Suppliers of Solubility Rig Components

Component	Part No.	Manufacturer/Supplier
Step down Adapter Consisting of; ¼" NPT stem Nut Washer	 RC0083 PC0023 PC0033	Welding Supplies Ltd. Unit 3, Albert Crescent, St. Philips, Bristol.
Female NPT thread ¼" to ¼"	ss-400-7-4	Swagelok make supplied by: Bristol Valve and Fitting Co., Fourth Way, Avonmouth, Bristol BS11 8DL.
Male Connector NPT thread 1/4" to 1/4" To connect to drying column	ss-400-1-4	Swagelok make supplied by; Bristol Valve and Fitting Co., Fourth Way, Avonmouth, Bristol BS11 8DL
Drying column	ss-304L-HDF4-1GAL	Whitey make supplied by: Bristol Valve and Fitting Co. Fourth Way, Avonmouth, Bristol BS11 8DL.
Union Tee 1/4" OD.	ss-400-3TTS	Swagelok Bristol Valve and Fitting Co. Fourth Way, Avonmouth. Bristol BS11 8DL.
Teledyne Compressed Air driven Pump (1000 bar)	_	George Meller Ltd, Orion Park, Northfield Avenue, Ealing, London W13 9SJ.
Connector for RV1 ¼" to ¼"	ss-400-6	Swagelok Bristol Valve and Fitting Co. Fourth Way, Avonmouth. Bristol BS11 8DL.
Relief Valve, RV1, set to lift at 60 bar,	ss-4R-3A.	Nupro make supplied by: Bristol Valve and Fitting Co. Fourth Way, Avonmouth, Bristol BS11 8DL.
Filter 1/4" 2μm size. I/4" (Male NPT inlet & outlet.)	ss-4TF2-ss-4F-K4-7	Nupro make supplied by: Bristol Valve and Fitting Co., Fourth Way, Avonmouth, Bristol BS11 8DL.
Tubing 1/4" OD, 0.08" thickness 20,000psi (1380bar) at 200°C	12m	Southampton Tube Sales, Majestic Road, Nursling, Southampton SO16 0AF.
Elbows 1/4"	ss-440-9	Snotrik fittings Bristol Valve and Fitting Co. Fourth Way, Avonmouth, Bristol BS11 8DL.
Connector for RV2 1/4"	15MX92R1	Autoclave Engineers Ltd. Supplied by:, George Meller Ltd Orion Park, Northfield Avenue Ealing, London W13 9SJ.
Relief Valve 2, RV2 Set to lift at 690 bar	10RVP9072	Autoclave Engineers Ltd. (same as above)
Pressure & Temperature Transducer	211-36-820-02	Paine Corporation, Seattle, USA; supplied by: Endeveco UK Ltd., Melbourne, Royston, Herts SG8 6NA.

Adapters for the Reaction Cell to fit 1/4" tubing. (3/8" to ¼")	ss-400-6-4	Bristol Valve and Fitting Co. Fourth Way, Avonmouth, Bristol BS11 8DL.
Reaction Cell Contructed by Smithkline Beecham Pharmcecticals	2"x 400mm 316 ss bar 4" x 200mm 316 ss bar (for the end caps)	Stainless steel bought from: Durbin Metal Industries, Bristol.
Pressure cell testing	N/A	Baskerville Ltd., 324c Barlow Moor Road, Chorlton-cum-Hardy, Manchester. M21 8AX
Pressure cell insurance		National Vulcan Engineering Insurance. St. Marys Parsonage, Manchester. M60 9AP
O rings and Back up rings (used for the end connectors)		Precision Polymer Engineering Ltd. Clarendon Road, Blackburn, Lancs., BB1 9SS.
High Pressure Valve, HV1, set to lift at 11000Psi.		Autoclave Engineers Ltd. Supplied by; George Meller Ltd, Orion Park, Northfield Avenue, Ealing, London W13 9SJ.
Throttle Valve, TV1,		Autoclave Engineers Ltd. Supplied by; George Meller Ltd. Orion Park, Northfield Avenue, Ealing, London W13 9SJ.
High Pressure Valve, HV3, pressure rated to 2070 bar.		Autoclave Engineers Ltd. Supplied by; George Meller Ltd, Orion Park, Northfield Avenue, Ealing, London W13 9SJ.
High Pressure Fittings (Snotrik Make)	Various	Bristol Valve and Fitting Co. Fourth Way, Avonmouth, Bristol BS11 8DL.
Low Pressure Valves.1/8"	ss-41TS2	Nupro type Bristol Valve and Fitting Co. Fourth Way, Avonmouth. Bristol BS11 8DL.
Flow meter.	1100series 1l/min	KDG Mobrey Ltd. Compton Way, Crawley, RH10 2YZ.
Temperature Indicators	normal thermometer	Not applicable.
Gas Meter.	GJF-452-L	Fisher Scientific, Loughborough. LE11 5RG.
Gallenkamp Plus II Oven	OVE-250-010C	Fisher Scientific, Loughborough. LE11 5RG.
Heat tracing element, used to maintain constant temperature in the high pressure region.	in-house	RS Components UK. Supplied by: Farnell Electronic Components Ltd, Canal Road, Leeds LS12 2TU.
Immersion Cooler Haake EK20 (-25 to +150°C)	BlB-385-010J	Fisher Scientific, Loughborough, LE11 5RG.
Grants Immersion cooler (-20 to +35°C)	BLE-510-010J	Fisher Scientific, Loughborough, LE11 5RG.
Magnetically Coupled Circulating Pump 14L/Min	RS 266-979	RS Components UK. Supplied by: Farnell Electronic Components Ltd, Canal Road, Leeds LS12 2TU.

AII.II Rig Costs

Items Bought

Steel Bar for the Equilibrium Cell	£116.00
Pump and Pump Controls (Teledyne Make)	£1284.00
Valves and Relief Valves	£2,300.00
Oven	£1610.00
Dry Gas Meter	£150.00
Pressure and Temperature Transducers and Adapters	£1902.00
Pressure and Temperature Transducers Display Unit	£224.07
High Pressure Tubing	£150.00
High Pressure Fittings	£1235.00
Low Pressure Fittings	£533.00
O-rings and Back up Rings	£64.00
Pressure and Temperature Meter	£311.00
Flowmeter	£338.00
Equilibrium Cell Testing	£1079.00
Heat Tracing and Controller	£202.56
Air Line	£24.00
Vent Pipe	£45.00
PC Data Acquisition	£1600
TOTAL:	**£13167.63**

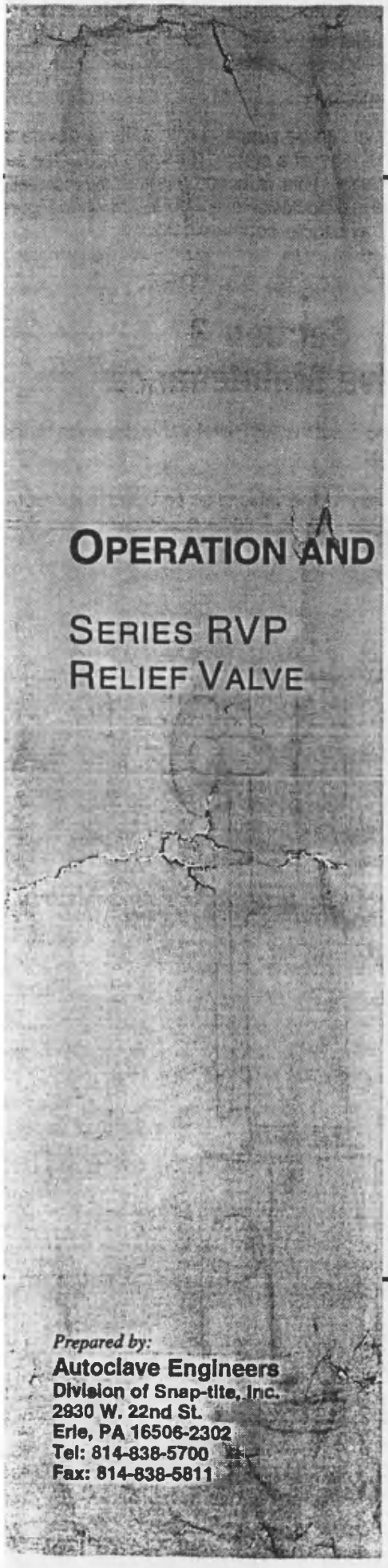
Thermoquest Service	£250
Chemicals from:	
Boehringer Ingelheim Ltd,	£1200
Shin- Estu Chemicals,	£180
Rohm Pharma.	£440
Carbon dioxide bottle £32 per month	£768
Consumables used	**£2838.00**

Items from the department or made in-house at no cost:
Drying Column, including Zeolite
Low Pressure Tubing
Glass U-tube Cold Trap
Speed Frame
Cooler Unit
Water Bath including antifreeze.

GRAND TOTAL **£16005.63.**

AII.III Relief Valve, RV2 – Operating Manual

(please turn over)



OPERATION AND MAINTENANCE MANUAL

SERIES RVP
RELIEF VALVE

CAUTION: WHILE TESTING HAS SHOWN O-RINGS TO PROVIDE SATISFACTORY SERVICE LIFE, BOTH CYCLIC AND SHELF LIFE MAY VARY WIDELY WITH DIFFERING SERVICE CONDITIONS. PROPERTIES OF REACTANTS PRESSURE AND TEMPERATURE CYCLING, AND AGE OF THE O-RING. FREQUENT INSPECTION SHOULD BE MADE TO DETECT ANY DETERIORATION AND O-RINGS REPLACED AS REQUIRED.

Prepared by:
Autoclave Engineers
Division of Snap-tite, Inc.
2930 W. 22nd St.
Erie, PA 16506-2302
Tel: 814-838-5700
Fax: 814-838-5811

ISO-9001
Certified

Section 1
Introduction

1.1 GENERAL INFORMATION

The Autoclave Engineers' Series RVP Relief Valve for gas or liquid service is designed to protect systems and components against over-pressure and to reclose after normal pressure conditions are reached.

1.2 SAFETY

The AE Relief Valve is factory tested for structural integrity and functionability. The valve's relieving pressure is pre-set at the factory and is sealed with a wire tie to assure proper valve operation when installed. The valve is also tagged with set pressure and a maximum allowable working pressure and temperature. Note that the relief valve flow characteristics are defined at an allowable accumulation of 10% over set pressure. It is good engineering practice to further protect against over-pressure with a rupture disc of sizeable area.

Section 2
Installation

2.1 INLET PIPING

The relief valve should be mounted in the vertical position and secured with mounting screws (customer supplied). The inlet tubing to the valve should be unobstructed and as short as possible between the item being protected and the relief valve.

Valves other than the relief valve should not be permitted in the relief line.

The inlet tubing should have an inside diameter of at least that of the relief valve nozzle, but never less than the calculated minimum required relieving area. All tubing should be clean and free of foreign matter and the connection to the valve should be clean and well-lubricated with an anti-galling substance (e.g., Jet Lube SS-30) before installation. The inlet connection should be tightened to the recommended torque value listed in AE's Catalog 6000.

2.2 OUTLET PIPING

The discharge piping from the relief valve should be direct and unobstructed. Where possible, a short discharge pipe is desirable. However, if this is impractical, consideration of back pressure must be made by the customer. In any case, the discharge pipe should be at least the same inside diameter as the relief valve discharge port.

2.3 SYSTEM TESTS

If it is desired to pressure test the system and/or components above the set pressure of the relief valve, a manual gagging device (1/4 -20 x 1.25" long hex socket cap screw) is supplied. The relief valve's maximum allowable working pressure must not be exceeded.

To manually gag the valve, remove the hex socket cap screw and gasket located on top of the valve cap. Store these items in a safe place. Make certain no back pressure exists at the valve outlet. Insert the gagging device and tighten to 40 in. lbs. Over-tightening could damage the valve.

After pressure testing is complete, remove the gagging device and replace the gasket and hex socket cap screw. Tighten to 90 in. lbs.

2.4 MANUAL VENTING

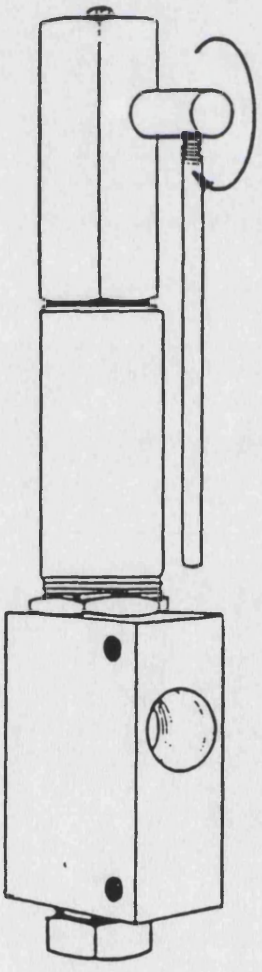
The AE Relief Valve can be supplied with a lifting device to manually open the valve at a system pressure below the set pressure of the valve. This is accomplished by manually rotating the handle in a clockwise direction as shown in Figure 1. Do not rotate the handle counterclockwise.

Section 3
Valve Maintenance

3.1 The operating life of the AE Relief Valve depends on the service conditions.

3.2 If it is necessary for the valve to be serviced, it is recommended that it be returned to Autoclave Engineers, Inc. Warranty is voided if seal is broken by customer.

Figure 1



Crucible Service Centers
A Divison of Crucible Materials Corporation

5639 W. Genesee St.
Camillus, NY
13031-0977

CERTIFICATE OF TEST

SNAP-TITE INC
2930 WEST 22ND STREET
ERIE PA 16506-2302

SHIPTO
SNAP-TITE INC
2930 WEST 22ND STREET
ERIE PA 16506-2302

CRUCIBLE ORDER NUMBER: 32-88088

DATE: 08/26/96

CUSTOMER ORDER # & DATE	CUSTOMER REQ. #	DISTRICT	SHIPPED FROM
30100-500 08/23/96		CLEVELAND	CLEVELAND

DESCRIPTION OF MATERIAL

1 316
Rectangle 316 SS .750 x 1.500 x RL CD Latest ASTM A276 (948)
Chemistry Only and ASME SA479 Strain Hardened Level II Except with
80 KSI Min Yield 25% Min Elongation 40% Min ROA DIN 50 049-3.1B
MS12-329

Intergranular Corrosion Test to Practice A - Ok

"Material is Free From Mercury Contamination and Alfa Radiation
at Time of Shipment."

"EN 10204-3.1B (DIN 50 049-3.1B) 926/931160-09371152.01 23 Jun 93
Approved by TUV Rheinland E.V."

MECHANICAL PROPERTIES

ITEM NO.	SIZE	QUANTITY	HEAT NO.	YIELD PSI	TENSILE PSI	%ELONG IN.	%RED AREA	HARDNESS	IMPACT
1	.750 X 1.500	147 LBS	A17689	89,130	132,465	32.50	69.90	BHN 229	

CHEMICAL PROPERTIES

HEAT NO.	C	MN	P	S	SI	NI	CR	V	W	MO	CU	CO	AL
A17689	0.0660	1.7200	0.0290	0.0240	0.6200	10.3200	16.6200			2.1200			
	N 0.0930												

CERTIFIED TRUE COPY
TEST CERTIFICATE
23/2/96

AUTOCLAVE ENGINEERS
Q. S. APPROVED
BY DNM
DATE 8/29/96

THE ABOVE MATERIAL WAS MANUFACTURED AND TESTED IN ACCORDANCE WITH THE ABOVE SPECIFICATIONS AND IS IN CONFORMANCE WITH THOSE SPECIFICATION REQUIREMENTS.

CRUCIBLE MATERIALS CORPORATION
ACTING BY AND THROUGH ITS SERVICE CENTERS DIVISION

168

CERTIFIED BY: Marilyn Nicholas
MARILYN NICHOLAS
QUALITY ASSURANCE REPRESENTATIVE

425.50

Crucible Service Centers
A Divison of Crucible Materials Corporation
5639 W. Genesee St.
Camillus, NY
13031-0977

QUALITY ASSURANCE CERTIFICATE OF TEST

		CRUCIBLE ORDER NUMBER
SNAP-TITE INC 2930 WEST 22ND STREET ERIE PA 16506-2302	SHIP TO: SNAP-TITE INC 2930 WEST 22ND STREET ERIE PA 16506-2302	32-88889
		DATE 10/17/96

CUSTOMER ORDER # & DATE	CUSTOMER REQ. #	DISTRICT	SHIPPED FROM
960100-520 09/12/96		CLEVELAND	CLEVELAND

DESCRIPTION OF MATERIAL

1 316
Rectangle 316 SS 1.000 x 2.500 x RL CD Latest ASTM A276 (95)
Chemistry Only and ASME SA479 Strain Hardened Level II Except with
80 KSI Min Yield, 25% Min Elongation, 40% Min ROA DIN 50 049-3.1B
MS12-325

Intergranular Corrosion Test Ok

"Material is Free From Mercury Contamination and Alfa Radiation
at Time of Shipment."

"EN 10204-3.1B (DIN 50 049-3.1B) 926/931160-D9371152.01 23 Jun 93
Approved by TUV Rheinland E.V."

MECHANICAL PROPERTIES

ITEM NO.	SIZE	QUANTITY	HEAT NO.	YIELD PSI	TENSILE PSI	%ELONG IN.	%RED AREA	HARD-NESS	IMPACT
1	1 X 2.500	768 LBS	A17881	96,942	113,960	29.00	71.10	BHN 241	

CHEMICAL PROPERTIES

HEAT NO.	C	MN	P	S	SI	NI	CR	V	W	MO	CU	CO	AL	N
A17881	0.0580	1.7600	0.0240	0.0220	0.4900	10.2400	16.4000			2.1600				0.0800

VERIFIED TRUE
TEST CERTIFICATE
23/12/96

AUTOCLAVE ENGINEERS
Q. C. APPROVED
10/18/96

THE ABOVE MATERIAL WAS MANUFACTURED AND TESTED IN ACCORDANCE WITH THE ABOVE SPECIFICATIONS AND IS IN CONFORMANCE WITH THOSE SPECIFICATION REQUIREMENTS.
CRUCIBLE MATERIALS CORPORATION
ACTING BY AND THROUGH ITS SERVICE CENTERS DIVISION

CERTIFIED BY Marilyn Nicholas
MARILYN NICHOLAS
QUALITY ASSURANCE REPRESENTATIVE

960100-520

SP 425.50

SNAP-TITE INC. AUTOCLAVE ENGINEERS
FLUID COMPONENTS DIVISION
ERIE, PENNSYLVANIA

Autoclave Engineers ISO 9001 Certified
QUALITY SYSTEM APPROVED

VALVE TEST REPORT
XCELL

CUSTOMER: GEORGE MELLER LTD

CUSTOMER ORDER NO.: 039495

PER AES/ESR #:

AE REGISTER NO#: 02-96202K9

DRAWING NO#: 304-2832

DESCRIPTION	QTY	PO NO.	HT NO.	HYDROSTATIC TEST		GAS TEST / SET PRESSURE		PACKING GLAND TORQUE (FT/LBS)	TYPE OF LUBE
				PSI	TIME (sec)	PSI	TIME (sec)		
BSW2021	1	960-100-520	A17881	16,500	15	11,000	15	40	J

CERTIFIED TRUE
TEST CERTIFICATE
23/12/96
Dated

☑ Accept ☐ Reject

If rejected, reason for failure

INSPECTOR: JZD QUALIFIED WITNESS: DATE: 11-26-96

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AII.IV Pressure and Temperature Transducers - assembly and calibration

(please turn over)

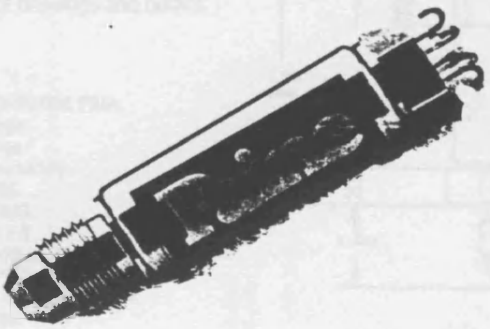
Downhole Series 211-37-520 & 211-36-820

0-3,500 through 0-25,000 PSIA. Designed for high temperature and high pressure application.

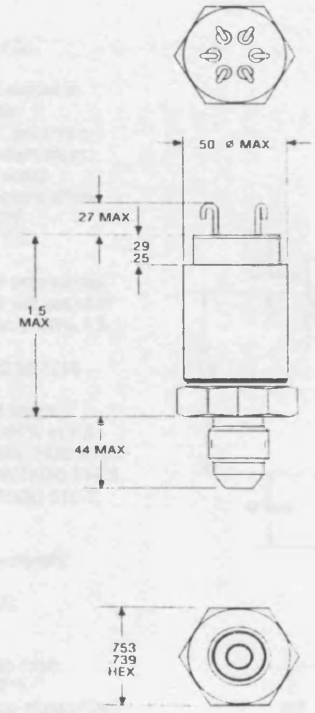
Specifically designed for high temperature and high pressure applications where long term stability is important. The material used in construction is compatible with H_2S and other highly corrosive media.

Instead of an o-ring, an Inconel 600 seal can be purchased and used for virtually maintenance-free, permanent installations. Contact the factory for drawings and details.

Notes and Specifications



1. Pressure range: 0-5,000 through 0-20,000 PSIA.
2. Proof pressure: 150% of rated range
3. Burst pressure: 200% of rated range
4. Excitation: 1 to 20 VDC (10 VDC nominal).
5. Input resistance: 1500 ± 300 OHMS.
6. Output resistance: 1500 ± 300 OHMS.
7. Output at zero pressure: 0 ± 2.0% F.S.
8. Full scale (F.S.) sensitivity: 2.6 mV/V ± .2%.
9. Operating temperature range: -40°F to +400°F.
10. Compensated temperature range: +75°F to +350°F.
11. Nonlinearity & hysteresis combined: ± 0.15% F.S., max. (B.S.L.M.).
12. Total error band including nonlinearity, hysteresis, and thermal effects: ± .75% F.S.
13. Stability & repeatability: A transducer tested per paragraphs 13.1 through 13.5 below will exhibit a zero balance and sensitivity stability within 0.1% F.S. from paragraph 13.1 to paragraph 13.5. Zero balance and sensitivity from paragraph 13.2 will repeat that of paragraph 13.4 within ± 0.1% F.S.
    - 13.1 Stabilize unit 4 hours at +100°F. Record output at 0 to 100% F.S. in 25% F.S. pressure steps.
    - 13.2 Stabilize unit 4 hours at +350°F. Record output at 0 to 100% F.S. in 25% F.S. pressure steps.
    - 13.3 Five pressure cycles from ambient to F.S. pressure and return. Hold 10 minutes at F.S. pressure steps.
    - 13.4 Within two hours after paragraph 13.3, record output at 0 to 100% F.S. in 25% F.S. pressure steps.
    - 13.5 Stabilize unit 12 hours minimum at +100°F. Record output at 0 to 100% F.S. in 25% F.S. pressure steps.
14. Sustained pressure/temperature stability: when pressurized to full scale pressure at 300°F, full scale output will not shift more than ± .03% F.S. in 14 days nor more than ± .05% F.S. in 60 days.
15. Pressure media: any compatible with Alloy UNS N07718 Rockwell C 40 max.
16. Environmental: error due to combined effect of shock, vibration, and acceleration shall be less than 0.01% of F.S. per G. Acceleration: 20 G's per MIL-STD-810, METHOD 513.3 PROC. I. Vibration: 20 G's per MIL-STD-810, METHOD 514.3, PROC. I. Shock: 30 G's per MIL-STD-810, METHOD 516.3, PROC. I.
17. Weight: 2.0 ounces max.
18. Electrical connections: Pin A (+excitation); B (+signal); C (-signal); D (-excitation); E (RTD); F (RTD)
19. Platinum resistance temperature detector (RTD): 0°C, 1000 Ω ± 2.5 Ω to ± IEC 751 ± .12%, Alpha = .00385 nominal.
20. Insulation resistance: all conductors together to case: 10,000 Megohms minimum at 50 VDC and +77°F.
21. Sustained pressure/temperature stability: When pressurized to full scale pressure at 350°F, full scale output will not shift more than .05% F.S. in 14 days nor more than ± .07% F.S. in 60 days.
22. For other configurations of this series, please contact the factory.



For more details, call toll free: 1.800.426.0366. 2401 South Bayview St. • Seattle, WA 98144
Phone 206.329.8600 Fax 206.329.1615 Email Painecorp @ aol.com

Downhole Series 211-37-520 & 211-36-820

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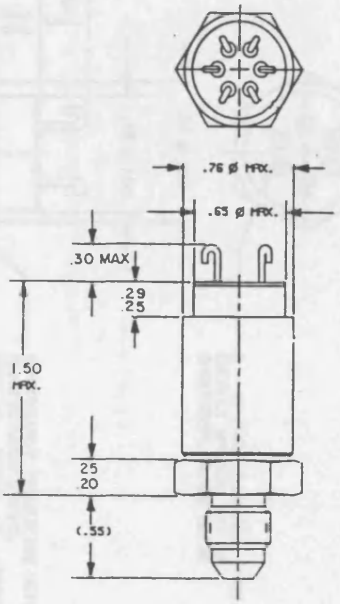

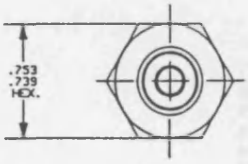

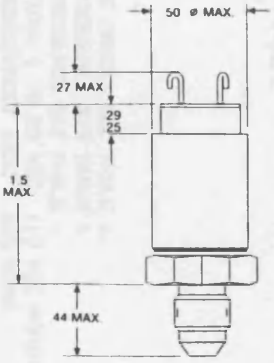

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17. Weight: 2.0 ounces max.
18. Electrical connections: Pin A (+excitation); B (+signal); C (-signal); D (-excitation); E (RTD); F (RTD).
19. Platinum resistance temperature detector (RTD): 0°C, 1000 Ω ± 2.5 Ω to ± IEC 751 ± .12%, Alpha = .00385 nominal.
20. Insulation resistance: all conductors together to case: 10,000 Megohms minimum at 50 VDC and +77°F.
21. Sustained pressure/temperature stability: When pressurized to full scale pressure at 350°F, full scale output will not shift more than .05% F.S. in 14 days nor more than ± .07% F.S. in 60 days.
22. For other configurations of this series, please contact the factory.

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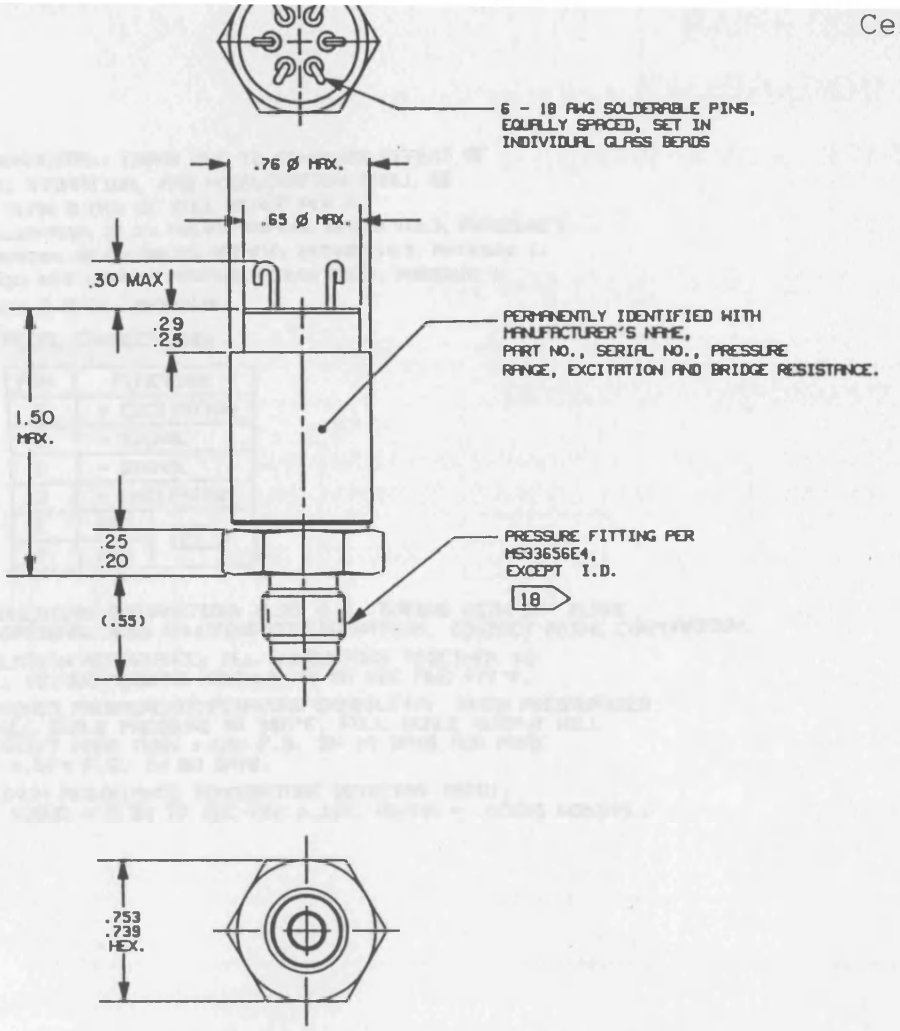

NOTES:

1 — PRESSURE RANGE: SEE TABLE I.
2 — PROOF PRESSURE: SEE TABLE I.
3 — BURST PRESSURE: SEE TABLE I.
4 — EXCITATION: 1 TO 20 VDC, (10 VDC NOMINAL).
5 — INPUT RESISTANCE: 1500 ± 300 OHMS.
6 — OUTPUT RESISTANCE: 1500 ± 150 OHMS.
7 — OUTPUT AT ZERO PRESSURE: 0 ± 2.0% FULL SCALE.
8 — FULL SCALE (F.S.) SENSITIVITY: 2.6 mV/V ± 0.2%.
9 — OPERATING TEMPERATURE RANGE: +75°F to +400°F.
10 — COMPENSATED TEMPERATURE RANGE: +75°F to +350°F.
11 — NON-LINEARITY AND HYSTERESIS COMBINED: ±0.15% F.S. MAXIMUM. (BEST STRAIGHT LINE METHOD).
12 — TOTAL ERROR BAND INCLUDING NON-LINEARITY, HYSTERESIS, AND THERMAL EFFECTS: ±.75% F.S..
13 — STABILITY & REPEATABILITY: A TRANSDUCER TESTED PER PARAGRAPHS 13.1 THROUGH 13.5 BELOW WILL EXHIBIT A ZERO BALANCE AND SENSITIVITY STABILITY WITHIN 0.1% F.S. FROM PARA. 13.1 TO PARA. 13.5. ZERO BALANCE AND SENSITIVITY FROM PARA. 13.2 WILL REPEAT THAT OF PARA. 13.4 WITHIN ± 0.1% F.S..

13.1 STABILIZE UNIT 4 HOURS AT +100°F. RECORD OUTPUT AT 0 to 100% F.S. IN 25% F.S. PRESSURE STEPS
13.2 STABILIZE UNIT 4 HOURS MINIMUM AT +350°F. RECORD OUTPUT AT 0 to 100% F.S. IN 25% F.S. PRESSURE STEPS.
13.3 FIVE PRESSURE CYCLES FROM AMBIENT TO F.S. PRESSURE AND RETURN. HOLD 10 MINUTES AT F.S. PRESSURE STEPS.
13.4 WITHIN 2 HOURS AFTER PARA. 13.3, RECORD OUTPUT AT 0 to 100% F.S. IN 25% F.S. PRESSURE STEPS
13.5 STABILIZE UNIT 12 HOURS MINIMUM AT +100°F. RECORD OUTPUT AT 0 to 100% F.S. IN 25% F.S. PRESSURE STEPS.

14 -- PRESSURE MEDIA: ANY COMPATIBLE WITH ALLOY UNS N07718 ROCKWELL C 40 MAX.

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TABLE I

PAINE CORP. PART NO.	PRESSURE RANGE	PROOF PRESSURE	BURST PRESSURE
211-36-820-01	0 - 5,000 PSIA	150%	200%
211-36-820-02	0 - 10,000 PSIA	150%	200%
211-36-820-03	0 - 15,000 PSIA	125%	150%
211-36-820-04	0 - 20,000 PSIA	125%	150%
211-36-820-05	0 - 3,500 PSIA	150%	200%

ENVELOPE DRAWING

	BY	DATE
DRAWN	ZZZ	11/7/89
CHECKED		
Q.A.		11/8/89
MFG		11/7/89
ENGRG		11/7/89
SALES		11/7/89
RELEASED		12 6 89

Paine Corporation
2401 South Bayview St., Seattle, WA 98144

TRANSDUCER, PRESSURE, ABSOLUTE

SIZE C | FSCM NO. 13624 | DWG NO. 211-36-820 | REV F
SCALE 2:1 | CFN B368201 | SHEET 1 OF 2

15 — ENVIRONMENTAL: ERROR DUE TO COMBINED EFFECT OF SHOCK, VIBRATION, AND ACCELERATION SHALL BE LESS THAN 0.01% OF FULL SCALE PER G.
ACCELERATION: 20 G's PER MIL-STD-810, METHOD 513.3, PROCEDURE I.
VIBRATION: 20 G's PER MIL-STD-810, METHOD 514.3, PROCEDURE I.
SHOCK: 30 G's PER MIL-STD-810, METHOD 516.3, PROCEDURE I.

16 — WEIGHT: 2.0 OZ. MAXIMUM.

17 — ELECTRICAL CONNECTIONS:

PIN	FUNCTION	
A	+ EXCITATION	
B	+ SIGNAL	
C	- SIGNAL	
D	- EXCITATION	
E	RTD	21
F	RTD	

18 INSTALLATION INFORMATION: 0.25 O.D. TUBING WITH 37° FLARE. FOR OPTIONAL BOSS MOUNTING CONFIGURATION, CONTACT PAINE CORPORATION.

19 — INSULATION RESISTANCE; ALL CONDUCTORS TOGETHER TO CASE: 10,000 MEGOHMS MINIMUM AT 50 VDC AND +77°F.

20 — SUSTAINED PRESSURE/TEMPERATURE STABILITY: WHEN PRESSURIZED TO FULL SCALE PRESSURE AT 350°F, FULL SCALE OUTPUT WILL NOT SHIFT MORE THAN ±.05% F.S. IN 14 DAYS NOR MORE THAN ±.07% F.S. IN 60 DAYS.

21 PLATINUM RESISTANCE TEMPERATURE DETECTOR (RTD): 0°C, 1000Ω ± 2.5Ω TO IEC 751 ±.12%, ALPHA = .00385 NOMINAL.

ENDEVCO U.K LTD

Melbourne, Royston, Herts
SG8 6AQ
Tel. Royston (01763) 261311
Facsimile (01763) 261120

ENVELOPE DRAWING

	BY	DATE
DRAWN		
CHECKED		
Q.A.		
MFG		
ENGRG		
APPD		
RELEASED		

Paine Corporation
2401 South Bayview St., Seattle, WA 98144

TRANSDUCER, PRESSURE, ABSOLUTE

SIZE	FSCM NO.	DWG NO.	REV
C	13624	211-36-820	F
SCALE ———		CFN B368202	SHEET 2 OF 2

PAINE CORPORATION

CALIBRATION CERTIFICATE

PART NUMBER: **211-36-820-02** Rev. F

PRESSURE RANGE: 0 to 10000 PSIA SERIAL NUMBER: **179308**

TEST EXCITATION: 10.00 VDC DATE TESTED: 8/9/96

PRESSURE CALIBRATION (mVDC)

PRESSURE (PSIA)	TEMPERATURE PERFORMANCE DATA							
	+75° F.		+150° F.		+250° F.		+350° F.	
	INCREASING PRESSURE	DECREASING PRESSURE	INCREASING PRESSURE	DECREASING PRESSURE	INCREASING PRESSURE	DECREASING PRESSURE	INCREASING PRESSURE	DECREASING PRESSURE
0	-.110	-.108	-.083	-.079	-.067	-.064	-.019	-.018
2000	5.073	5.083	5.106	5.116	5.127	5.137	5.182	5.189
4000	10.268	10.280	10.304	10.319	10.333	10.345	10.392	10.403
6000	15.474	15.486	15.516	15.529	15.550	15.561	15.615	15.626
8000	20.689	20.697	20.735	20.746	20.778	20.785	20.851	20.857
10000	25.915	-------	25.969	-------	26.015	-------	26.097	-------
RTD (in ohms)	1092.8		1254.6		1466.6		1673.4	

INPUT RESISTANCE: *1596.0* Ohms

OUTPUT RESISTANCE: *1532.0* Ohms

INSULATION RESISTANCE: *> 10000 Megohms at 50 VDC*

*STATIC ERROR (.150% F.S. max.): *.070% F.S.*

*TOTAL ERROR BAND (±.75% F.S. max.): .75%

PROOF PRESSURE: *15000 PSI*

BURST PRESSURE: *20000 PSI*

NOTE: All tests performed at 75° F. ± 5° F. except as noted.
Unit calibrated using PSIG pressure steps. The barometric offset has been subtracted from all readings.

ENDEVCO U.K LTD
Melbourne, Royston, Herts
SG8 6AQ
Tel. Royston (01763) 261311
Facsimile (01763) 261120

Quality Assurance
PAINE CORPORATION

ELECTRICAL CONNECTIONS	
PIN	FUNCTION
A	+ Input power
B	+ Signal
C	- Signal
D	- Input power
E	RTD
F	RTD

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CALIBRATION CERTIFICATE

PART NUMBER: **211-36-820-02** Rev. F

PRESSURE RANGE: 0 to 10000 PSIA SERIAL NUMBER: **179307**

TEST EXCITATION: 10.00 VDC DATE TESTED: 8/9/96

PRESSURE CALIBRATION (mVDC) 65.56°C 121.11°C 176.67°C

	PRESSURE	23.89°C TEMPERATURE PERFORMANCE DATA							
		+75° F.		+150° F.		+250° F.		+350° F.	
GAR	(PSIA)	INCREASING PRESSURE	DECREASING PRESSURE	INCREASING PRESSURE	DECREASING PRESSURE	INCREASING PRESSURE	DECREASING PRESSURE	INCREASING PRESSURE	DECREASING PRESSURE
∅	0	-.062	-.058	-.056	-.052	-.066	-.063	-.036	-.034
137.893	2000	5.122	5.140	5.133	5.151	5.129	5.145	5.163	5.176
275.786	4000	10.318	10.342	10.332	10.357	10.333	10.356	10.371	10.394
413.68	6000	15.524	15.546	15.543	15.567	15.549	15.570	15.594	15.614
551.57	8000	20.741	20.755	20.765	20.781	20.780	20.791	20.830	20.840
689.47	10000	25.969	-------	25.999	-------	26.016	-------	26.073	-------
	RTD (in ohms)	1091.6		1253.6		1465.6		1671.6	

INPUT RESISTANCE: *1625.0* Ohms

OUTPUT RESISTANCE: *1531.0* Ohms

INSULATION RESISTANCE: *> 10000 Megohms at 50 VDC*

*STATIC ERROR (.150% F.S. max.): *.070% F.S.*

*TOTAL ERROR BAND (±.75% F.S. max.): .46%

PROOF PRESSURE: *15000 PSI*

BURST PRESSURE: *20000 PSI*

NOTE: All tests performed at 75° F. ± 5° F. except as noted.
Unit calibrated using PSIG pressure steps. The barometric offset has been subtracted from all readings.

ENDEVCO U.K LTD
Melbourne, Royston, Herts
SG8 6AQ
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Jon Chesshew
Quality Assurance
PAINE CORPORATION

ELECTRICAL CONNECTIONS	
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A	+ Input power
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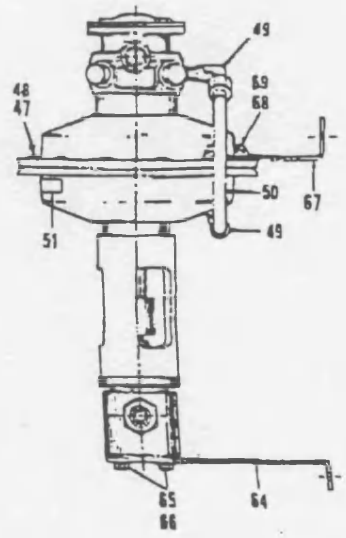
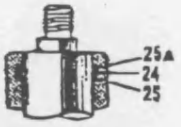
AII.V Technical drawings of the Equilibrium Cell.

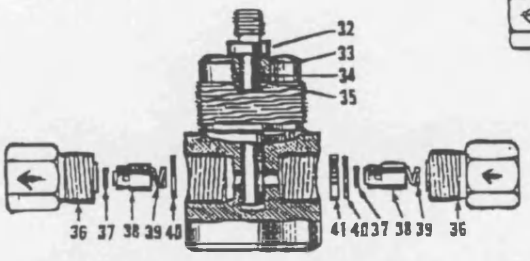
(please turn over)





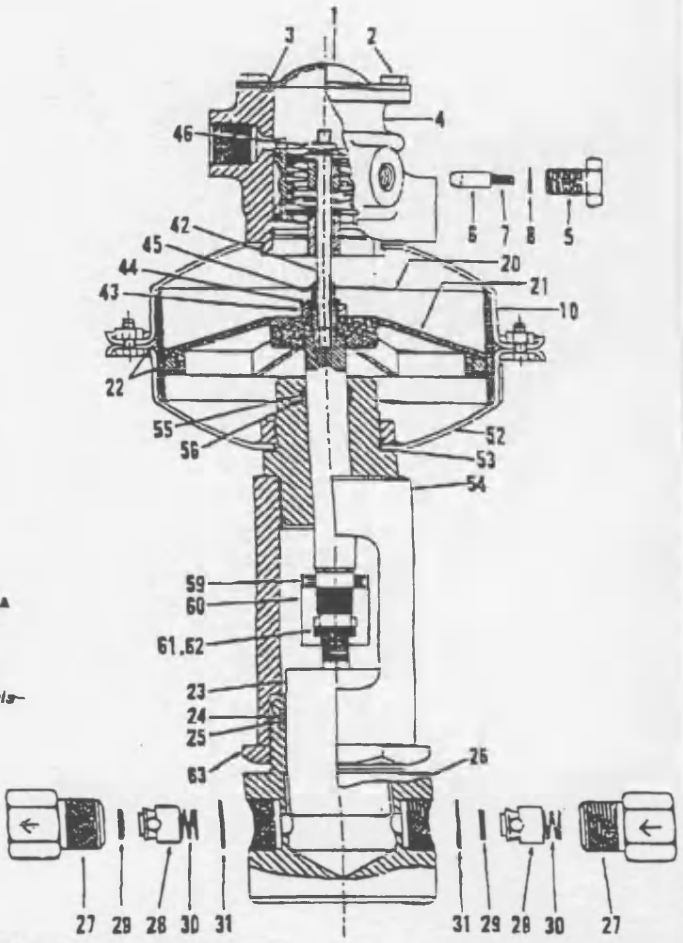
Fluid Body/Piston Seals– for 35:1 to 200:1 ratio pumps.

Fluid Body/Piston Seals– for 300:1 ratio pumps.



INLET Check Valve Assembly OUTLET Check Valve Assembly

200:1 to 300:1 Ratio Pumps– with liquid body/piston seals for 35:1 to 300:1 ratio pumps.



INLET Check Valve Assembly OUTLET Check Valve Assembly

10:1 to 150:1 Ratio Pumps– with liquid body/piston seals for 10:1 to 30:1 ratio pumps.

*Seals are available for Neoprene, Viton, EPR and for water service.

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George Meller Limited

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****PRODUCT DESCRIPTION****

Teledyne Fluid System

Model No.	S216-JS-150
Part No.	77896-31154
Date	A3Q95
PSIG	16000 (Maximum Outlet Pressure)
PSIG	100 (Maximum Drive Pressure)